SPECIAL SECTION

EVALUATION and REHABILITATION of LONG COVID

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INTRODUCTION
People with COVID-19 who have “persistent symptoms, or the onset of long-term symptoms, ≥ 4 weeks after acute COVID-19” are contending with post-acute sequelae of SARS-CoV-2 (PASC), or Long COVID. An important Centers for Disease Control and Prevention (CDC) study used a matched cohort design to search the medical records of about 1,640,000 controls and 353,000 case patients during March 2020–November 2021. The authors looked for 26 post-COVID conditions, including the pulmonary, cardiac, neurologic, gastrointestinal, renal, hematologic, and musculoskeletal systems. At least one condition related to the viral infection was present in 20% of COVID-19 survivors aged 18–64 years and 25% who were ≥65 years. In the older population, the relative risk was at or more than 1.5 for pulmonary emboli, respiratory symptoms, renal failure, thromboembolic events, fatigue, acute myocardial infarction, myopathies, neurologic conditions, Type 2 diabetes, smell/taste disturbance, and cardiac dysrhythmias (listed in decreasing incidence). These conditions are all linked by angiotensin converting enzyme 2 (ACE2), which acts as a functional receptor on cell surfaces for SARS-CoV-2 to invade the cells. “ACE2 expression occurs in alveolar, bronchial/respiratory, myocardial, breast, endothelial, arterial smooth muscle, tongue, esophageal, stomach, ileum, colon, rectum, renal proximal tubule, bladder, testicular, uterus, ovarian, and maternal-fetal cells as well as neurons and glia, cholangiocytes, adipose tissue, and pancreatic exocrine glands and islets.”

In view of the aggressive and invasive nature of the SARS-CoV-2 virus, which attacks multiple organ systems and causes a widespread inflammatory and pro-thrombotic state, it is not surprising that patients develop Long COVID. Furthermore, the lingering presence of the virus is associated with PASC. Endoscopic studies of small and large intestinal tissue in patients with inflammatory bowel disease (IBD) seven months after mild acute COVID-19 found SARS-CoV-2 RNA in 70% and viral nucleocapsid protein in 52% (but negative viral cultures). Patients with these viral antigens had multiple symptoms of Long COVID, including chest pain (3.1%), myalgias, palpitations, depression, dyspnea, coughing, diarrhea, sleep disorders, headaches, abdominal pain, anosmia, memory issues, and fatigue (56.3%). At least one symptom was present in 65.6% of patients who had persistent viral antigen – but none in the group with no viral antigen after the infection. The authors hypothesized that “viral antigen persistence instigates immune perturbation” and “serves as a basis for post-acute COVID-19.”

Test data show that 88.4 million Americans have been infected with COVID-19, which means that about 18–20 million people (20–25%, based on CDC findings) are affected by a variety of medical/surgical conditions included in PASC. Amid diverse symptoms and multisystem damage, it is important to search for patterns and classifications. A prospective study found three distinct groups with Long COVID symptoms. Cluster 1 often had pain symptoms, including joint pain, myalgias, and headaches. Cluster 2 had mainly cardiovascular symptoms (chest pain, shortness of breath, palpitations). Cluster 3 was characterized by the lowest number of symptoms and the least disability, with fatigue and dyspnea as the most common conditions. There were fewer symptoms in Cluster 3 than Cluster 1 (2 vs. 6 per patient). As expected, the first two clusters showed greater functional and respiratory impairment, vocational disability, and lower scores of general health. The authors felt that classifying patients could reveal different pathophysiologic mechanisms and improve the assessment and treatment of Long COVID. On the other hand, it is essential to be alert...
Figure 2. Effect of SARS-CoV-2 infection on different organs of the human body

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for unusual clusters of organ involvement, as in the following case report of a patient with cognitive, olfactory, cardiac, pulmonary, musculoskeletal, neuropathic, gynecologic, sleep, and psychological conditions that are part of her Long COVID syndrome.

CASE REPORT
A 51-year-old woman (with Moderna vaccination in April, May, and November 2021) tested positive for COVID-19 on January 1, 2022. Her symptoms included nasal congestion, laryngitis [with vocal loss for two days], dyspnea, tachycardia, chest pain, exhaustion, alternating warmth/chills, and severe weakness that made her arms feel extremely heavy. Her condition worsened due to tachycardia and orthostasis that caused two syncopal episodes. On January 10, 2022 her blood pressure was 90/60 [her baseline is 130/80]. Her lab studies showed an elevated white cell count [13.1 k/μL]; increased neutrophils [10.27, up to 8 is normal]; C-reactive protein level of 6 mg/L [normal is less than 5]; an elevated LDH [222 U/L, up to 214 is normal]; and a D-dimer level of 3.72 μg/mL [less than 0.51 is normal]. She was diagnosed with multiple symptoms related to COVID-19, including postural orthostatic tachycardia syndrome (POTS), for which she was placed on metoprolol (25 mg twice a day). She continued to feel severe fatigue, as if her body were weighed down with lead. To maintain her blood pressure, she was given compression stockings and advised to hydrate herself with a 50% solution of Gatorade and water [5 glasses a day minimum].

Additional evaluations during January and February 2022 included a stress test, Holter monitor, and a pulmonary function test. During an inconclusive stress test, she achieved only 60% of her predicted exercise capacity [a few minutes, up to 4.7 METs]; her blood pressure rose from 100/60 to 112/62 and her pulse from 71 to 100 [with a blunted response due to metoprolol]. The 48-hour Holter monitor showed primarily a sinus rhythm with a pulse ranging from 56–113; minimal atrial and ventricular ectopy; a few ventricular triplets; and no symptoms [while on metoprolol]. Her pulmonary function test showed normal lung volumes, but with increased residual volumes and diffusion capacity, and a positive methacholine challenge that was “suggestive of reactive airways” [and likely related to COVID-19]. She was started on a steroid inhaler (beclomethasone).

In a telemedicine evaluation on February 18, 2022 [Long COVID phase, six weeks after symptom onset], I learned that she was contending with neuropathic symptoms: “buzzing” in her hands and feet as well as a sensation of painfully tight gloves; her feet improved to some extent with compression socks. “Brain fog” affected her short-term memory and her ability to concentrate. Due to her cognitive impairment, on occasion she made errors like mailing the wrong document and missing an exit while driving – even with the use of her GPS. She had chronic fatigue and her activity level was generally impaired; some mornings she was unable to get out of bed, although she did have a few good days. Her cough had mostly resolved but left her with chest pain related to costochondritis. Her past medical history included back pain, irritable bowel syndrome, depression, dysmenorrhea and decreased endurance with exercise [but no diagnosis of asthma and no use of inhalers].

When I examined her in June 2022, she was using her steroid inhaler twice a day and occasional albuterol [since April] as a rescue dose – for reactive airway symptoms caused by COVID-19. After not menstruating for years while on Junel, she had irregular bleeding during March but it resolved after stopping her medication for a week. Compression stockings, hydration, and metoprolol [now 12.5 mg in the morning and 25 mg at night] had helped her chest pain and palpitations; she switched to taking her night dose two hours before going to sleep, to prevent supine tachycardia. She had insomnia before the viral infection, but Long COVID worsened her sleep pattern due to tachycardia [until metoprolol took effect] and neuropathic discomfort in her hands.
POTS and dehydration caused two episodes of passing out in one night; in one of these falls, a bracelet cut her wrist and her glasses caused an injury below an eye. She still had an uncomfortable “buzzing” sensation in her hands, but it was no longer constant. The post-COVID fatigue had decreased her activity level and therefore she had gained some weight. Some days, she felt “wiped out” and her arms felt “incredibly heavy.” Recently, she rode her bicycle for 20 minutes for the first time since her infection and was extremely fatigued the next day. She had persistent cognitive impairment, especially with retrieving new material such as numbers or bits of information that she had just thought of, heard, or read. Despite these problems, she was able to work on a part-time basis (editing, consulting on policy matters, preparing reports).

Due to these persistent symptoms, she was referred to a rehabilitation program [3 times a week for 2–3 months] and a monthly Long COVID support group. A 6-minute walk test showed a baseline blood pressure of 112/64, 99% oxygen saturation, and a pulse of 78. At two minutes, her oxygen saturation declined to 93%. She walked at a rate of 2.3 miles per hour [2.8 METs]; her fatigue level went from a baseline of 6 to 8; and she felt very tired as she had not slept well the previous night. Mental health surveys revealed that her level of depression was low; her anxiety was moderate; and her overall level of stress was high.

The examination revealed that she had no problems with her gait pattern and climbing steps. Vital signs while seated were pulse 68 and blood pressure 117/80, which changed to 80 and 107/75 [with no orthostatic symptoms] after standing. Her cranial nerves (2–12) were normal with visual acuity, extraocular movements, jaw and facial muscle function, facial sensation, hearing, palatal elevation, sternocleidomastoid and trapezius function, and tongue movements. Her olfactory sense was impaired; she misperceived the scent of cloves as cinnamon and could not smell vanilla and almond essences. Muscle strength was 5/5 at the shoulders, elbows, wrists, hands, hips, knees, and ankles; her tone was normal. The sensory examination revealed normal light touch, proprioception, and vibratory sense in all extremities. Reflexes were normal in the upper extremities, but decreased at the patellar and Achilles tendons. Her plantar responses were down-going. The cerebellar exam showed that she had normal finger-to-nose, rapid alternating movements, and heel-to-shin testing. She had a normal Romberg test. Range of motion at the shoulders, elbows, wrists, hands, hips, knees, and ankles was normal. Her lungs were clear to auscultation and her cardiac examination revealed a normal rhythm with no murmurs.

Cognitive testing with the Repeatable Battery for the Assessment of Neuropsychological Status showed that her score with learning a list of words was 30/40 and with recalling a short story was 15/24; copying a complex figure gave a score of 18/20; assessing the angles of intersecting lines was 17/20; naming fruits and vegetables in one minute was 18/40; recalling strings of digits was 11/16; matching symbols to numbers was 33/89; recalling the initial list was 7/10; and recalling the complex figure was 10/20. Her lowest score was in the domain of Attention [recalling strings of digits and matching symbols to numbers]. Her highest scores were in the Immediate Memory and the Visual Spatial-Constructional domains, but were only at the 50th percentile for her age group. The composite score for all these subs tests placed her in the 34th percentile of cognitive function. This result was clearly a decline from her baseline. She had graduated from Brown University, obtained an MSW degree, and then taught courses in writing and communication as an adjunct professor at two universities. At present, she works as an independent education consultant and freelance writer. She is diligent with her physical rehabilitation and has developed her own strategies for cognitive rehabilitation.

This case report is representative of patients with Long COVID, who can experience a variety of symptoms after disease onset. It also describes the diagnostic testing that many patients go through, often with minimal or no abnormal findings. Objective evidence that was consistent with Long COVID in this patient included elevated D-dimer, white blood cell, and C-reactive protein levels as well as orthostasis (POTS), a positive methacholine challenge, and a decline in oxygen saturation – more than four weeks after the acute infection. In many respects, Long COVID is a diagnosis of exclusion as patients and their providers search for explanations and treatable causes for their symptoms. Frequently, the symptoms outweigh the objective findings, and this can be frustrating and challenging for both patients and their physicians.

**PUBLIC HEALTH ISSUES**

It is vital that the healthcare system has clinicians who strive to understand, treat, and conduct research on the post-acute sequelae of COVID-19. At present, patients with Long COVID are eligible for rehabilitation along the entire spectrum of care. Depending on their clinical needs, which are associated with insurance criteria, patients can receive acute inpatient rehabilitation [3 hours/day of therapy]; subacute rehabilitation [1–1.5 hours/day of therapy]; home care [therapy 3 times a week]; and outpatient rehabilitation [3 times a week]. In the context of this public health crisis of disability, health care professionals and organizations should develop systems of care for the entire spectrum of Long COVID, with specialized clinics where clinicians can see large numbers of patients to improve their treatment for this complex syndrome and carry out essential research studies. Patients should also receive education about multisystem issues with Long COVID, including how to monitor themselves [e.g., self-oximetry], adapt, and improve their quality of life. Support groups through specialized clinics and online
communities, such as Survivor Corps, are also essential for long-term success in dealing with the myriad problems of Long COVID.7

Rhode Island and Brown University have been at the forefront of the pandemic, through the public health perspectives of Dr. Megan Ranney and Dr. Ashish Jha. We are also fortunate to have physicians like the authors in this special issue of the Rhode Island Medical Journal, who have contributed their invaluable clinical experience and knowledge of the latest medical literature on Long COVID. This issue includes articles on pulmonary, cardiac, neurological, cognitive, and orthopedic complications of Long COVID. As our knowledge of this syndrome evolves, we will need to address all the bodily systems that are vulnerable due to the ubiquitous presence of ACE2, which functions as a doorway for SARS-CoV-2. From the public health perspective, it is important to note that the US Department of Health and Human Services states that “Long COVID can be a disability under Titles II [state and local government] and III [public accommodations] of the Americans with Disabilities Act, Section 504 of the Rehabilitation Act of 1973, and Section 1557 of the Patient Protection and Affordable Care Act. Each of these federal laws protects people with disabilities from discrimination.”8 These legal protections and governmental support will be essential for clinicians, caregivers, and survivors with Long COVID.

References

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Disclosure
Dr. Mukand is working on a nonfiction narrative/self-help book about Long COVID and would like to interview people on the full spectrum of severity and conditions, especially visual, GI, hepatic, renal, skin, and musculoskeletal complications.

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A Review of Respiratory Post-Acute Sequelae of COVID-19 (PASC) and the Potential Benefits of Pulmonary Rehabilitation

MICHAEL SIMON, MD; JAMES E. SIMMONS, MD

ABSTRACT
With the SARS-CoV-2 pandemic continuing into its third year, the number of patients who survive acute COVID-19 infection but go on to develop long-term symptoms is increasing daily. Those individuals who experience one or more of a variety of persistent symptoms post-COVID-19 are now diagnosed with the syndrome called post-acute sequelae of COVID-19 [PASC], often colloquially called “Long COVID.” This article discusses relevant research and current hypotheses regarding the pathophysiology and management of respiratory symptoms of PASC, in order to provide primary care physicians with context for management of this heterogeneous population. We focus on the growing body of research that supports the use of pulmonary rehabilitation for patients with PASC to improve symptoms and quality of life.

KEYWORDS: post-acute sequelae of COVID-19; PASC; Long COVID; pulmonary rehabilitation

INTRODUCTION
COVID-19 is the disease caused by the SARS-CoV-2 virus, which was first identified in December 2019 in China.¹ The subsequent pandemic has had an immeasurable impact on humanity and claimed the lives of over 6 million people. The majority of patients infected with SARS-CoV-2 [up to 80%] will only experience mild acute disease, but still roughly 10% to 35% of these patients, as well as up to 86% of patients with moderate to severe acute COVID-19, will develop various long-term symptoms.¹⁻³ This syndrome is now termed post-acute sequelae of COVID-19 [PASC] and is also known colloquially as “Long COVID.” We will review the current definitions and pathophysiologic understanding of PASC and then discuss the diagnostic and management strategies for people suffering with respiratory symptoms.

POST-ACUTE SEQUELAE OF COVID-19 (PASC)
More than two years since the discovery of SARS-CoV-2, we are only beginning to understand its long-term effects. With each passing variant and subsequent wave of infections, the number of patients who shift from acute infection to the post-acute syndrome increases. Though far from complete, the literature is beginning to coalesce around a definition for stratifying patients with persistent symptoms after the acute COVID-19 infection has resolved. Symptoms continuing beyond four weeks from the onset of COVID-19 are considered to be post-acute COVID-19.⁴ When symptoms persist, the Centers for Disease Control and Prevention (CDC) define PASC as occurring in “individuals with a history of probable or confirmed SARS CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis.”⁵ Many patients with severe acute COVID-19 requiring supplemental oxygen, hospitalization, or even mechanical ventilation are unsurprisingly burdened with long-term symptoms, but PASC can also be seen in patients who were never hospitalized for acute COVID-19 and had only mild symptoms initially. Symptoms of PASC vary significantly in quality, severity, and organ system involvement. Dyspnea is the most common respiratory complaint, occurring in 15% of non-hospitalized patients and up to 81% of hospitalized patients.⁶ Other commonly cited respiratory complaints include cough, chest pain, or decreased exercise tolerance.⁶⁻⁶⁻⁸ Non-respiratory symptoms include low-grade fevers, headaches, neurocognitive difficulty, muscle pain and weakness, gastrointestinal symptoms, rashes, thromboembolic conditions, depression, and post-traumatic stress disorder. In a study of non-hospitalized post-COVID-19 patients from Germany, 30% had at least one symptom [anosmia, ageusia, fatigue, or dyspnea] at four months.⁹ Beyond the known negative impact on quality of life (QOL) metrics, PASC presents an ongoing challenge for the public health system of this country.¹⁰⁻¹²

Although some post-acute symptoms can likely be attributed to the effects of the virus, other long-term symptoms are less clear. For example, it is well established that acute COVID-19 results in a pro-thrombotic state as compared to other viral illnesses, and resultant pulmonary emboli can lead to significant post-COVID breathlessness. The more insidious symptoms of fatigue, deconditioning, “brain fog,” and psychiatric sequelae are not as well understood. The burden of disease is not only a consequence of somatic complaints, but also a decline in overall QOL.¹¹ There are several hypotheses for why these downstream disorders occur. Some have suggested that the deconditioning is
The viral tropism of SARS-CoV-2, or more simply the number of different cell types it can infect, lends credence to the idea that the post-acute phase of infection affects multiple systems. Specifically, SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2), which functions as a receptor, in order to enter cells; this protein is expressed not just in the entire human respiratory system but also in the brain, gastrointestinal tract, and pancreatic beta-cells. Other hypotheses include residual organ damage, remaining viral reservoirs, and the possible confounding variable of post-critical illness (especially myopathy and neuropathy) for those who required intensive care. In all, it is likely there are multiple pathways that lead to PASC, as broadly defined, and future studies should focus on delineating subgroups of PASC for diagnostic and management purposes.

**RISK FACTORS FOR PASC**

With such a broad definition and varied clinical picture for PASC, primary care physicians (PCPs) must have a low threshold to consider PASC in patients after COVID-19 infection, regardless of the initial severity and especially when there are identifiable risk factors. Much of the literature to date has focused on the chronic sequelae following severe COVID-19 infection, which have proposed pathophysiologic origins supported by prior known mechanisms of acute respiratory distress syndrome. Of particular interest to primary care physicians are the impact and long-term consequences of mild or even asymptomatic COVID-19 infection. In a systematic review of patients who experienced a mild infection in the outpatient setting across Europe and the United States, between 10% and 35% of these patients still had symptoms after the acute phase of illness. Furthermore, in one of the largest studies included in this comprehensive review, less than 1% of patients reported being symptom-free at three months.

Clearly, PASC can occur in anyone following COVID-19, and although establishing a comprehensive list of risk factors for developing PASC will likely require years of additional study, the current literature describes some clear associations. Smoking status, elevated body mass index, cancer, older age, and pre-existing chronic respiratory disease are all associated with worse acute outcomes as well as long-term sequelae. However, it is unclear how they factor into the prognostication of patients who experienced initial mild versus severe disease. In a recent systematic review and meta-analysis, a significant association was found between female sex and any reported chronic symptom (OR 1.52; 95% CI 1.27–1.82). It has been hypothesized that females may have a protective genetic milieu against COVID-19 that is on the X chromosome, so that men are more likely to succumb to the acute illness and not develop long-term consequences. Diabetes mellitus type 2, a high COVID viral RNA load, Epstein-Barr virus reactivation, and certain investigational autoantibodies are additionally implicated as possible risk factors. In fact, in this study there was an association between particular autoantibody patterns and specific PASC symptoms. Patients with elevated levels of the IFN-alpha2 antibody were uniquely associated with respiratory symptoms of PASC, even after correcting for other factors. This may lead to the development of biomarkers that could guide the clinical management of PASC.

**RESPIRATORY SEQUELAE**

While the burden of symptoms from PASC should be appreciated through a multisystem lens, the most disabling problems in PASC are fatigue and breathlessness, so the remainder of this article will focus on these aspects and the importance of pulmonary rehabilitation. The respiratory symptoms of patients with PASC are varied, and there is emerging evidence of at least two clinical subgroups that may benefit from different management strategies. The first is characterized by fibrotic lung changes that are visible on imaging and a restrictive pattern on pulmonary function testing (PFTs), with or without diffusion capacity impairment (like the patient in Figure 1). The other subgroup has more acute inflammatory findings on radiography, with potentially reversible damage that may be steroid-responsive. These cases are similar to the chronic disease seen after the first SARS virus outbreak, Middle East respiratory syndrome (MERS), and H1N1 influenza. Current evidence suggests that only some patients in either group have persistent physiologic or radiographic changes that can help guide therapy. Conversely, the burden of symptoms does not always correlate to these standard measures of pulmonary function, as seen in many patients with severe respiratory symptoms of PASC who have normal PFTs and lung imaging. This makes it clear that management decisions must be individualized for PASC patients.

Currently, it appears that most patients will have a slow improvement of respiratory PASC, and although the rate can vary dramatically between weeks to months, a majority have symptom resolution three months after the diagnosis of PASC. Although a systematic review of respiratory function in post-acute COVID-19 found that diffusion capacity...
was abnormal in 39% of patients, the PFT abnormalities decreased in incidence over time. This suggests that the timing of a pulmonary function testing is important to establish a new baseline as the lungs heal, though no practice pattern has been validated to this point.

**RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS**

Internists and family practitioners are typically the frontline physicians who manage these patients. Although we should consider PASC in post-COVID-19 patients, it is also important to remember the new axiom that “all that appears long-haul is not COVID.” A reasonable workup to rule out confounding, concomitant, or alternative diagnoses distinct from PASC should be undertaken to evaluate persistent symptoms following COVID-19 infection. While guidelines are scarce, there appears to be some agreement regarding evaluations for patients with respiratory symptoms of PASC. These include chest radiograph, PFTs, and six-minute walking distance (6MWD) testing at 12 weeks post-infection for baseline measurement. Further evaluation with high resolution computed tomography (HRCT) or echocardiography following evidence of residual infiltrates on chest radiograph should be done in association with referral to appropriate specialists.

Supplemental oxygen should be prescribed to patients who have resting or exertional hypoxemia (generally oxygen saturation <88%) as in other chronic lung diseases; many patients do improve their DLCO, so the need for oxygen should be re-evaluated after two to three months. The diagnostic and therapeutic management of chronic lung disease following COVID-19 is beyond the scope of this article, as there is not yet consensus on many of the difficult clinical decisions that arise for these patients. This speaks to the broader consensus that an interdisciplinary care model is likely to be most beneficial. In that context, if patients have radiographic or PFT abnormalities that correlate to respiratory symptoms or a patient requires supplemental oxygen, then it is reasonable to involve a pulmonologist to determine the need for medical therapies such as systemic steroids for possible inflammatory lung disease, bronchodilators for airways disease, or evaluation for neuromuscular disease.

**PULMONARY REHABILITATION**

Pulmonary rehabilitation (PR) has emerged as a safe and effective intervention that can be offered to patients with shortness of breath lasting four weeks after confirmed or suspected COVID-19 infection; Medicare covers reimbursement for this indication. PR is defined as “a multidisciplinary intervention based on personalized evaluation and treatment which includes, but is not limited to, exercise training, education, and behavioral modification designed to improve the physical and psychological condition of people with respiratory disease.”

In our two years of caring for PASC patients in The Miriam Hospital Center for Cardiac, Pulmonary and Vascular Fitness PR program, we have seen many remarkable cases of significant improvement in QOL measures and dyspnea scores after our 12-week program. This includes two visits a week for individualized and monitored exercise as well as interdisciplinary interventions such as a COVID support group and psychosocial supports. Past patients have included those who were treated for acute respiratory distress related to COVID-19 in an intensive care unit for weeks and survived with chronic supplemental oxygen and tracheostomies, but there are also many previously healthy young patients with mild to moderate acute COVID-19. One such patient was a 40-year-old female marathon runner who developed such significant dyspnea on exertion that she could barely walk across the room despite normal oxygen requirements, PFTs, and chest imaging. Both types of patients had significant improvements in their dyspnea, their QOL based on standard PR measures, and exercise tolerance as measured by 6MWD, despite likely different
pathophysiologic mechanisms. Anecdotally, overall adverse events for these PASC patients do not appear significantly different from the other chronic lung disease patients we have managed for years.

Our experience has been confirmed by mounting scientific evidence that PR is beneficial for PASC patients with respiratory symptoms. While there has not been an established minimal clinical important difference (MCID) for improvement of 6MWD in survivors of COVID-19, the studies in a meta-analysis by Chen et al surpassed the accepted 30 meters for MCID in other chronic lung disease. Specifically, the pooled estimate of improvement was 50.41 meters—despite some studies not including endurance training, which may underestimate the true impact of pulmonary rehabilitation.31 In another study, patients with mild to moderate COVID-19 infection were able to increase 6MWD by 47 meters, despite PR occurring six months after the initial infection.32 This encouraging finding supports the benefit of rehabilitation in parallel with the natural recovery process, even if the infection was fairly remote. More recent studies have built on this finding with an impressive number needed to treat of 1.26 to achieve a one-grade improvement in a post-COVID-19 functional status scale.33 There are many mechanisms by which PR may benefit these patients with more than just their respiratory complaints, as described in Figure 2.

While the SARS-CoV-2 virus will likely become endemic in our microbiologic ecosystem, we continue to grapple with the consequences of the pandemic. Encouragingly, the respiratory symptoms of PASC show the promise of improvement through pulmonary rehabilitation. With each passing day, the number of COVID survivors increases, and even though a significant number will suffer from long-term consequences of the infection, we also gain new insights into the diagnosis and management of PASC through the ongoing efforts of researchers and clinicians globally.

References


Figure 2. Potential Benefits of Exercise on the Most Frequent Clinical Manifestations of post-COVID-19 syndrome


Long-term Cardiovascular Manifestations and Complications of COVID-19: Spectrum and Approach to Diagnosis and Management

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ABSTRACT
Survivors of coronavirus disease 2019 (COVID-19) may experience persistent symptoms, abnormal diagnostic test findings, incident disease in specific organ systems, or progression of existing disease. Post-acute COVID-19 syndrome (PACS) is defined by persistent, recurrent, or new symptoms, findings, or diagnoses beyond four weeks after the initial infection. PACS has been characterized as a multi-organ syndrome, often with cardiopulmonary symptoms that include fatigue, dyspnea, chest pain, and palpitations. Cardiovascular pathologies in PACS include new-onset arrhythmia, myocarditis, unmasked coronary artery disease, and diastolic dysfunction as well as abnormal findings on electrocardiogram, troponin testing, and cardiac magnetic resonance imaging. In this review, we discuss the cardiovascular symptoms, pathophysiology, clinical investigation, and management strategies for cardiopulmonary symptoms of PACS. We offer a treatment algorithm for primary care clinicians encountering patients with cardiopulmonary PACS and discuss ongoing research on this topic.

KEYWORDS: Post-acute COVID-19 syndrome; Long COVID; Post-Acute Sequelae of SARS-CoV-2; PASC; PACS; cardiovascular disease; CVD

BACKGROUND
Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2, or COVID-19] is characterized by both pulmonary and extrapulmonary manifestations, with acute cardiovascular effects including thromboembolic events, new-onset heart failure, myocardial infarction, and arrhythmias. There is growing recognition that some individuals may endure post-acute COVID-19 syndrome [PACS], defined by persistent, recurring, or new symptoms, signs, and/or diagnoses attributable to COVID-19 that extend beyond the acute phase [four weeks after onset of infection].1 PACS, also known as post-acute sequelae of COVID-19 [PASC] or Long COVID, is a multi-organ syndrome that often has persistent cardiopulmonary symptoms including fatigue, dyspnea, chest pain, and palpitations.2 PACS encompasses an array of new cardiovascular and other end-organ pathologies or progression/exacerbation of preexisting cardiopulmonary conditions. Cardiovascular pathologies in PACS may include new-onset arrhythmia, myocarditis, and diastolic dysfunction as well as abnormal findings on electrocardiogram [ECG], troponin testing, and cardiac magnetic resonance imaging [CMR] [in relation to specific clinical diagnosis or long-term clinical outcomes].2-7 Figure 1 provides an overview of PACS manifestations as it relates to the cardiovascular system. As more individuals, numbering in the millions, are infected by SARS-CoV-2 and survive the acute phase, it is of significant societal importance to understand the long-term sequelae of this disease.

In this review, we discuss the cardiovascular symptoms and pathophysiology of PACS, current clinical investigation and management strategies for cardiopulmonary symptoms of PACS, and ongoing investigations of cardiopulmonary PACS.

Figure 1. Spectrum of cardiovascular symptoms, signs, and/or diagnoses observed in post-acute COVID-19 syndrome

BP—blood pressure; CAD—coronary artery disease; CMR—cardiac magnetic resonance imaging; CPET—cardiopulmonary exercise testing; ECG—electrocardiogram; HF—heart failure; JVD—jugular venous distention; LE—lower extremity; MI—myocardial infarction; PACS—post-acute COVID-19 syndrome; VTE—venous thromboembolism.
CARDIOVASCULAR SYMPTOMS OF PACS

Beyond the first 30 days of illness, COVID-19 survivors, both those who required hospitalization and those with milder cases, have reported a broad range of cardiovascular symptoms, including dyspnea, chest pain, palpitations, dizziness and tachycardia (Table 1). Ramadan et al summarized the findings of 20 studies, with median time to assessment of 52 days post-COVID diagnosis, and noted dyspnea (median 33%; range 0–87%), chest pain (median 17.5%, range 0–73%), and palpitations (median 0.77; range 0–88%). Prolonged symptoms were significantly associated with hospitalization for initial COVID-19.

Table 1. Common cardiovascular symptoms and risk factors observed in patients experiencing post-acute COVID-19 syndrome.*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Older Age</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Higher BMI</td>
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<tr>
<td>Chest Pain</td>
<td>Female Gender</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Pre-COVID Cardiovascular Disease (CAD, HF, Arrhythmias)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Pre-COVID Comorbidities (DM, HTN, CKD, Chronic Lung Disease)</td>
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<tr>
<td>Tachycardia</td>
<td>Initial Symptomatic COVID-19 Illness</td>
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<tr>
<td>Exercise Intolerance</td>
<td>Limited Baseline Functional Status</td>
</tr>
</tbody>
</table>

*Table based on data reported by the American College of Cardiology and the American Heart Association task force and expert consensus groups.

CARDIOVASCULAR PATHOLOGIES IN PACS

The various cardiovascular diseases that may be diagnosed in patients experiencing PACS, along with their relative frequencies highlighted with color coding, are shown in Figure 2.

PACS and arrhythmias

Arrhythmias have been identified both during the acute phase of infection and as part of PACS. Arrhythmia is one of the most common cardiac symptoms during acute COVID-19. Coromillas et al found that the majority of patients with arrhythmias during acute COVID-19 did not have a prior history of arrhythmia. Of those who did develop an arrhythmia, the majority (81.8%) had atrial arrhythmias, 20.7% had ventricular arrhythmias, and 22.6% had bradyarrhythmias. However, Ingul et al performed 24-hour EKGs on patients 3–4 months after COVID-19 and detected arrhythmias in 27% of patients, with PVCs as the most common arrhythmia. Musikantow et al retrospectively studied the incidence of atrial fibrillation and flutter in over 5,000 hospitalized patients with COVID-19 or influenza, and found similar rates in both groups, with an association between arrhythmia and elevations in inflammatory markers, myocardial injury, and death. The results suggest that atrial fibrillation and flutter during COVID-19 hospitalization may occur secondary to severe systemic disease.

EKG changes including T-wave abnormalities, ST segment depression, right bundle branch block, and sinus tachycardia have been identified. These changes were mainly observed in studies assessing patients less than three months after diagnosis or recovery from the acute phase of COVID-19. Xie et al analyzed 153,760 US Veterans diagnosed with COVID-19 who survived for 30 days and found an increased 1-year risk of dysrhythmias (including sinus tachycardia, sinus bradycardia, atrial and ventricular arrhythmias) compared to a large population-based control group [comparative hazard ratio [HR] 1.69, 95% confidence interval [CI] 1.64–1.75]. A possible mechanism for post-COVID arrhythmias is myocardial damage from the inflammatory cascade and subsequent fibrosis, remodeling, and arrhythmias.

PACS and inflammatory heart disease

Myocardial and pericardial inflammation can be seen both in the acute phase of COVID-19 and in the post-acute phase. Xie et al found that beyond 30 days after infection with...
SARS-CoV-2, individuals had a much higher relative risk of myocarditis [HR 5.38; 95% CI 3.80–7.59] and pericarditis [HR 1.85; 95% CI 1.61–2.13] compared to control cohorts. Several studies have identified high rates of cardiac inflammation and pericardial enhancement on CMR up to six months post-hospitalization. Cardiac findings on CMR include increased T1 and T2 intensity, late gadolinium enhancement, and pericardial effusion. Although initial studies found high rates of abnormalities on CMR, particularly among athletes recovering from COVID-19, few patients reported cardiovascular-related symptoms during follow-up. Further, when evaluating autopsy results, only 1.2% met histological criteria for myocarditis. CMR findings of myocarditis do not always seem to correlate with patient symptoms, calling into question its clinical significance. Similarly, it appears that small pericardial effusions are relatively common in the post-acute period of COVID-19, but symptomatic pericarditis is rare.

**PACS, cardiac injury, and ischemic heart disease**
Myocardial injury with elevated troponins, ischemia and infarction have been described in acute and post-acute COVID-19. Several mechanisms of myocardial injury in the setting of COVID-19 have been hypothesized, including a proinflammatory state from cytokine storm, direct viral invasion of myocytes, hypercoagulable state with thromboembolic phenomenon, coronary plaque instability, demand-supply mismatch with increased demand from systemic inflammation, and accelerated atherosclerosis and plaque rupture. In the post-acute phase of COVID-19, the cytokine-mediated damage can cause thrombogenesis, decreased oxygen supply, coronary plaque destabilization, progression of chronic cardiovascular disease (CVD) into unstable disease, increased metabolic demand, and reduced cardiac reserve. One study found that patients with COVID-19 had a three times higher likelihood of a major adverse cardiac event at a median of five months post-discharge compared to controls matched by age, sex, and risk factors. The one-year incidence rates of ischemic heart disease, including acute coronary disease [HR 1.72; 95% CI 1.56–1.90], myocardial infarction [HR 1.63; 95% CI 1.51–1.75], and ischemic cardiomyopathy [HR 1.75 (95% CI 1.44–2.13)] are all increased when compared to a control cohort without COVID-19.

**PACS, heart failure and cardiomyopathy**
COVID-19 has been associated with several echocardiographic abnormalities. Right ventricular dysfunction, likely secondary to pulmonary disease, was the most common finding. Other abnormalities include regional left ventricular (LV) systolic dysfunction, diastolic dysfunction, global hypokinesis, left ventricular hypertrophy, and pulmonary hypertension. Xie et al found that patients with COVID-19 had a significantly higher one-year risk of incident heart failure [HR 1.72; 95% CI 1.65–1.80] than control patients. Another study found an increased trend in Takatsubo cardiomyopathy both in the general population and in COVID-19 patients during the pandemic, thought to be secondary to isolation and stress as well as SARS-CoV-2 infection and illness. Furthermore, patients with underlying heart failure are particularly vulnerable to disease exacerbation, progression, and decompensation in the post-acute period of COVID-19.

**PACS and dysautonomia**
Cardiovascular autonomic dysfunction can be seen post-COVID, and it has been described as a postural orthostatic tachycardia syndrome (POTS)-like illness or orthostatic intolerance. POTS has been suggested as a possible etiology for symptoms of chest pain, palpitations, and dizziness in patients with post-acute COVID-19 syndrome.

**PACS and thromboembolism**
Several studies have identified increased rates of thromboembolic events in both the acute and post-acute phases of COVID-19. In the post-acute phase, Xie et al found a significantly increased risk of deep vein thrombosis (HR 1.98; 95% CI 1.94–2.24), pulmonary embolism (HR = 2.93; 95% CI 2.73–3.15), and superficial vein thrombosis (HR=1.95, 95% CI 1.80–2.12) in patients who survived beyond 30 days after COVID-19 diagnosis. A retrospective study that followed COVID-19 patients up to 30 days post discharge found that 2.5% had a thrombotic event including pulmonary embolism, intracardiac thrombus, and ischemic stroke.

**PACS, pulmonary hypertension, and right heart failure**
COVID-19 has been associated with pulmonary hypertension and right heart failure in those hospitalized during the acute phase of the disease. Multiple mechanisms for developing pulmonary hypertension have been postulated, including inflammation, cytokine storm, endothelial injury, hypercoagulability causing venous thromboembolism, thrombotic microangiopathy, and vasoconstriction. These pathophysiologic mechanisms are postulated to lead to either pre-capillary pulmonary hypertension or chronic thromboembolic pulmonary hypertension. Additionally, pulmonary hypertension may be a result of hypoxia and significant lung injury from the acute disease. However, data on pulmonary hypertension and right heart failure as long-term manifestations of PACS are limited.

**CURRENT CLINICAL MANAGEMENT STRATEGIES**
As the number of COVID-19 survivors experiencing PACS continues to grow, clinical management strategies for the evaluation and treatment of cardiopulmonary symptoms are necessary. Ongoing treatment-focused clinical trials will ideally refine these strategies (Table 1). Currently, however,
there is limited clinical guidance for clinicians to manage patients with cardiopulmonary symptoms attributed to PACS. Among professional societies, the European Society of Cardiology published a position paper in October 2021, offering strategies for outpatient cardiologists in the initial evaluation of PACS patients. Clinical management algorithms have also been published.44,45 In May 2022, the American College of Cardiology Consensus Decision Pathway gave guidelines on cardiovascular sequelae of COVID-19 in adults, including myocardial involvement, cardiovascular manifestations of PACS, and return-to-play for professional and non-professional athletes.44 In this review, we propose a clinical algorithm for patients with cardiopulmonary symptoms and signs after the acute phase of COVID-19 (Figure 3).

The diagnosis of PACS can be made in a variety of healthcare settings. Among early studies of patient cohorts in multidisciplinary PACS clinics, clinicians found that some cardiopulmonary symptoms and complications after COVID-19 were not always proportional to the severity of the acute disease.46 However, disease severity in general has emerged as a predictor of PACS cardiopulmonary symptoms and complications.19,47 Referrals to cardiovascular or PACS clinics are not necessarily dependent on the severity of the acute disease. Referral is especially important for patients with cardiovascular comorbidities and manifestations of PACS, given their increased risk of morbidity and mortality.7,48

Due to the cardiovascular burden of COVID-19, current guidance tailors the clinical history, vital signs, and physical examination to search for new arrhythmias, POTS, myo- and pericarditis, heart failure, and unmasked coronary artery disease.44-46,49 Universal cardiovascular testing strategies have also been considered; among athletes with persistent cardiopulmonary symptoms attributed to PACS, the American College of Cardiology guidelines for determining return-to-play recommended “trial testing” with EKG, high-sensitivity troponin, and echocardiography.14

Balancing the investigation of cardiopulmonary symptoms after acute COVID-19 against the potential risks of false-positive findings and overdiagnosis, we agree with symptoms-based diagnostic evaluation that adheres to professional guidelines.44,45,50 The range of testing for cardiopulmonary PACS is broad, and includes imaging, cardiac biomarkers, and even cardiac catheterization. Cardiopulmonary symptoms, particularly in PACS, pose a diagnostic challenge in determining if they are primarily attributable to cardiovascular or pulmonary pathology.45 Careful diagnostic testing that addresses positive and negative findings of both cardiovascular and pulmonary disease, such as echocardiography and chest computed tomography, will assist clinicians in evaluating patients with PACS. In patients with unexplained persistent cardiopulmonary symptoms, cardiopulmonary exercise testing (CPET) may identify objective abnormalities and classify them as cardiac, vascular, pulmonary, muscular, or some combination of multisystem involvement; this will allow a more directed approach to treatment.51

The management of cardiopulmonary diseases linked to PACS, including acute coronary syndrome, pulmonary embolism, and myocarditis, has largely been informed by established professional guidelines. Treatment recommendations for persistent symptoms, in the current investigational landscape, are primarily supportive.44,45 Multiple treatment algorithms suggest cardiopulmonary rehabilitation, if without contraindication, as well as mental health counseling.43,45,52 Another algorithm noted the potential overlap between cardiopulmonary symptoms of PACS and deconditioning attributable to acute COVID-19, with a
recommendation for graduated exercise regimens, including recumbent or semi-recumbent exercises (e.g., swimming) for those with significant postural symptoms. Other standard pharmacological and nonpharmacological approaches (e.g., compression stockings, midodrine, beta-blockers) may help patients with autonomic dysregulation (e.g., orthostatic hypotension, inappropriate sinus tachycardia, POTS, palpitations). Clinicians may also consider screening PACS patients with questionnaires for depression and anxiety, such as the Patient Health Questionnaire-9 and the General Anxiety Disorder-7; both conditions have been associated with PACS, may exacerbate symptoms, and are linked to cardiovascular disease. All clinicians caring for PACS patients with persisting cardiopulmonary symptoms should recommend COVID-19 vaccination if without contraindications, given the association of vaccination with improvement in PACS symptoms demonstrated in prior studies.

**ONGOING TRIALS AND FUTURE DIRECTIONS**

Moving forward, research priorities for cardiopulmonary problems of PACS should include: clarifying the pathophysiology of PACS; identifying patient populations that are vulnerable to cardiopulmonary PACS (as well as specific risk factors); and developing treatment modalities for PACS. Numerous trials are currently investigating cardiovascular outcomes in patients with PACS. Treatment trials for cardiopulmonary PACS have focused on the effects of cardiac and pulmonary rehabilitation, though metoprolol succinate for PACS symptoms is also under investigation. Additionally, since the start of the COVID-19 pandemic, researchers globally have recruited large cohorts of individuals with a history of COVID-19 for further investigations into cardiovascular outcomes associated with PACS. Multidisciplinary PACS clinics are foundational to research efforts, serving as referral centers to benefit patients as well as to recruit longitudinal cohorts for the epidemiologic study of PACS. Such efforts should be supported by public and private funding for advancing clinical understanding and treatment strategies, including pharmacologic management, for cardiopulmonary disease associated with PACS.

Despite strong public interest and its significance to population health, PACS research will continue to face substantial challenges. The nature of PACS as a disease, characterized by persisting symptoms frequently without a readily identifiable pathophysiology, may prove difficult to measure and diagnose. For measurement, the utilization of remote patient monitoring data may offer new opportunities for PACS research, such as in investigations of arrhythmia or cardiopulmonary symptom burden. The clinical course of cardiopulmonary PACS may ultimately differ by variants implicated in the initial infection. More broadly, observational studies for PACS research would benefit from uniform eligibility criteria, with comparator groups that have negative SARS-CoV-2 testing, and geographic and temporal comparability. Specifying uniform entry criteria between cases and controls will help ensure that these studies are able to elucidate the causal nature of long-term CVD complications arising in survivors of acute COVID-19.

**CONCLUSION**

PACS, defined by the persistence or recurrence of symptoms or diagnoses attributable to COVID-19 beyond four weeks after initial infection, is increasingly recognized among COVID-19 survivors. Cardiopulmonary manifestations include persistent dysrhythmias, inflammatory disease, ischemic disease, heart failure, and dysautonomia. Current clinical management strategies for cardiopulmonary PACS emphasize diagnostic pursuit of symptoms based on clinical history, vital signs, and physical exam, as well as focused diagnostic testing starting with EKG. Athletes and those in high-risk or strenuous occupations may benefit from troponin testing and echocardiogram in their initial evaluation. Treatment for symptoms of cardiopulmonary PACS largely involves graded exercise and supportive measures, while new or worsening cardiovascular disease should be treated in accordance with best-practice guidelines. Numerous trials for cardiopulmonary PACS treatment are ongoing, primarily focused on the role of cardiopulmonary rehabilitation.

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EVALUATION & REHABILITATION OF LONG COVID

Neurological Sequelae of COVID-19 in Rehabilitation Settings

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ABSTRACT
Neurological symptoms of post-acute sequelae of COVID-19 [PASC], also known as Long COVID, are recognized. Four neurological syndromes [transverse myelitis, ischemic stroke, headache, and Guillain-Barré syndrome] associated with PASC are reviewed here, with a particular focus on issues related to rehabilitation.

KEYWORDS: Long COVID, neurological, rehabilitation

INTRODUCTION
The World Health Organization (WHO) defines Long COVID as symptoms lasting at least two months after a probable or confirmed diagnosis of COVID-19, usually starting within three months of COVID-19 onset.1 This syndrome is also described as post-acute sequelae of COVID-19 (PASC). Neurological symptoms of PASC are variable and include fatigue, cognitive impairment, headache, myalgia, sensorimotor abnormalities, seizures, and dysautonomia.1,2 Several neurological syndromes have been described in relation to PASC. In the absence of specific evidence for these syndromes, their treatment typically proceeds according to that for similar but non-COVID-related entities. For example, COVID-19-associated Guillain-Barré Syndrome (GBS) is treated in the same way as pre-pandemic GBS. Due to the prolonged symptoms in some COVID-19 cases, rehabilitation strategies are increasingly used to improve outcomes and hasten recovery.

In this review, we focus on four COVID-19-associated neurological syndromes that may benefit from inpatient or outpatient rehabilitation. These include GBS, transverse myelitis (TM), ischemic stroke, and headache. We will discuss the typical clinical presentation, theorized pathophysiology of these syndromes, and potential rehabilitation needs and treatments.

TRANSVERSE MYELITIS
Transverse myelitis (TM) is focal inflammation of the spinal cord, resulting in neurologic deficits [weakness, sensory loss, bowel/bladder dysfunction]. Common causes include multiple sclerosis, neuromyelitis optical spectrum disorder [NMOSD], myelin oligodendrocyte glycoprotein associated disease [MOGAD], and neurosarcoidosis. A handful of cases of TM have been reported in the context of PASC,3,8 and there are two theorized mechanisms for this condition. The first postulates viral invasion of the CNS via the ACE2 receptors on the brain/spinal glial cells and the endothelial cells of the blood brain barrier. The second proposed mechanism is a post-infectious autoimmune mediated response.3

TM presents clinically with acute to subacute focal neurologic deficits that correlate to the area of spinal cord inflammation. COVID-19-associated TM has been seen in both the acute phase of the illness as well as up to one month after the acute COVID-19 phase.4,7 This time frame would support the proposed pathophysiology of direct viral invasion and post-inflammatory autoimmune response, respectively.

On MRI scans, both longitudinally extensive spinal cord lesions and multifocal cord lesions have been described in COVID-19-related TM. The cervical and thoracic segments of the spinal cord are most often implicated, and within the cord the ventral horns are most commonly affected. The ventral horn predominance correlates with patients typically presenting with primarily motor symptoms. Notably, this ventral horn predominance is also seen in other viruses that infect the spinal cord directly [e.g., polio, flaviviruses, and enterovirus].3 The standard treatment of TM, including that associated with COVID-19, consists of high-dose steroids and frequently the addition of either plasmapheresis or intravenous immunoglobulin (IVIG). Patients with COVID-19-associated TM had various degrees of clinical improvement. One report showed complete recovery after a course of steroids and IVIG,3 but most cases with COVID-19 TM do not fully recover over the first several days and require physical rehabilitation.

Given the small number of case reports describing TM with PASC, there are limited data regarding specific rehabilitation outcomes. In non-COVID TM, long-term follow up shows that approximately one-third of patients recover with minimal to no impairment; one-third have moderate disability [e.g., independent ambulation with mild spasticity, some manageable urinary/bowel changes, sensory deficits]; and one-third have severe disability [e.g., inability to walk independently, no sphincter control].9 The aim of physical rehabilitation in these patients is to maximize their independence and capabilities. Physical and occupational therapists focus on strength and range-of-motion to improve...
tone, mitigate pain, and maximize functional mobility and independence with daily activities. Generally, in spinal cord injury rehabilitation, individuals with an injury at or below T12 may regain independent ambulation with assistive devices. Patients with cervical and high-thoracic lesions do not have as good a prognosis for ambulation. TM associated with COVID-19 is typically of the cervical and thoracic segments, but the outcomes data for this cohort are insufficient to make any generalizations about the prognosis for ambulation. Regardless, it is important to begin rehabilitation early and aggressively as about a third of patients with TM have a chance of near complete recovery. Furthermore, the recovery process for TM can go on for a year or more, so it is important to periodically re-evaluate patients for additional courses of physical and occupational therapy. Overall, it appears that Long COVID-associated TM patients who are treated early on with high-dose steroids and IVIG in conjunction with a physical rehabilitation program will have the best prognosis and a chance for full recovery.

**ISCHEMIC STROKE**

Ischemic strokes have been associated with COVID-19. A systematic review during the first six months of the pandemic showed that the average incidence of ischemic stroke in COVID-19 patients was 1.5%,11 and a retrospective cohort study (March to April 2020) showed a 0.9% incidence of stroke, with a disproportionate number having strokes of uncertain etiology [cryptogenic].12

The theorized mechanisms of COVID-19-associated ischemic stroke are cardiomyopathy and/or hypercoagulability.11,13 This hypercoagulability includes elevated D-dimer and fibrinogen levels or fibrin/fibrinogen degradation products as well as elevated pro-inflammatory cytokine levels and direct damage to endothelial cells.11,13 In an early study, patients with COVID-19 had a much higher incidence of cryptogenic strokes as compared to non-COVID-19 patients.12

Depending on the location of the cerebral infarct, ischemic stroke can present with a variety of symptoms. Rehabilitation must be tailored to a patient’s unique needs by an interdisciplinary team. Rehabilitation treatments after non-COVID stroke focus on improving mobility and activities of daily living (ADLs), often by helping patients practice and relearn basic activities.14,15 The rehabilitation team will also address bowel and bladder function, pain management, psychological issues, and education of the patient and family. Most clinical recovery takes place in the first 3-6 months after stroke.14

There are no data about rehabilitation in patients with stroke related to COVID-19. An important consideration in discussing rehabilitation approaches is that patients with stroke in the context of COVID-19 had more severe strokes at admission and worse functional outcomes than those without the viral infection.16 Therefore, they are likely to require more intensive and longer periods of inpatient rehabilitation.

**HEADACHE**

Headache is one of the most common neurological symptoms of COVID-19.17,18 In patients with acute COVID-19, 11–34% reported a headache, and 5–55% of patients experienced headaches three months after the acute infection.19 There is no known pathophysiology for these headaches, but a plausible mechanism is the release of cytokines and chemokines by macrophages during infection.20 It is also theorized that the SARS-CoV-2 virus may activate trigeminal nerve endings, directly or indirectly, via vasculopathy and/or circulating cytokines/chemokines.21

The headaches described in COVID-19 are usually bitemporal, pressure-like or pulsatile, and may have associated migrainous photophobia/phonophobia.19,21,22 They usually occur on a daily basis and are more prevalent in patients with underlying medical comorbidities (hypertension, coronary artery disease, diabetes, and hypothyroidism).17 They are also difficult to control with standard treatments for tension or migraine headaches.

In some instances, COVID-19-associated headaches are refractory to standard management, and there is increasing interest in an interdisciplinary approach, similar to post-concussion headache management. There is wide variation in the structure of concussion clinics, but most have some combination of specialists in neurology, physical medicine and rehabilitation, sports medicine, social work, physical therapy, occupational therapy, and psychology.23 In interdisciplinary concussion clinics, these clinicians work together to treat the complex causes of post-concussive headaches. The Mayo Clinic has been introducing Long COVID patients with headaches to their Brain Rehabilitation clinic that previously was reserved for concussion patients. Using the concussion clinic as a model, the interdisciplinary management of Long COVID headaches may be the best option for rehabilitation of these patients.

**GUILLAIN-BARRÉ SYNDROME**

Guillain-Barré Syndrome (GBS) is an autoimmune peripheral polyneuropathy characterized by ascending weakness and/or sensory loss.24 Pre-pandemic GBS was frequently a post-infectious illness associated with campylobacter jejuni as well as Epstein Barr virus, mycoplasma pneumonia, Haemophilus influenzae and influenza A. It is thought to be caused by molecular mimicry, the theory in which foreign antigens have structural similarities to self-antigens and thereby trigger an autoimmune reaction.24

GBS associated with COVID-19 is considered primarily a post-infectious syndrome, but some studies have also shown...
a para-infectious variant. 

Molecular mimicry is the postulated pathological mechanism of GBS, and a study by Lucchese and Floel showed this mimicry between COVID-19 and human heat shock proteins. The mechanism in the less frequent, para-infectious variant of COVID-19-associated GBS is thought to be caused by direct injury to nerves and/or an underlying immunodeficiency.

As in conventional patients with GBS, those with COVID-19 are most often treated with IVIG or plasmapheresis. Follow-up and outcome data on patients with COVID-19 are limited, but a review noted that in an unspecified “short” time interval, 62% of patients with GBS had significantly improved or recovered. Radisic et al showed that there was no difference in disability score between GBS patients with or without COVID-19 at three months after hospital discharge. In a study of eight patients, Solaro et al showed that COVID-19-associated GBS had better outcomes than non-COVID-19 GBS.

There are limited data on rehabilitation methods and outcomes for patients with COVID-19-associated GBS, but most case reports suggest an interdisciplinary approach with physical, occupational and speech/swallow therapy. Rehabilitation in these cases has mainly focused on functional training for safety and independence through exercises for strength, balance, and range-of-motion.

Data on the rehabilitation of non-COVID-related GBS may be helpful. A study by Prada et al showed that continuing physical therapy for more than six months can improve functional outcomes in GBS. A randomized controlled trial by Khan et al showed that at 12 months, patients with high intensity rehabilitation (three 1-hour sessions per week with PT, OT, psychology and speech therapy) scored better on scales of functional status and their perception of the disease.

**CONCLUSION**

COVID-19 can be associated with long-lasting neurologic symptoms. In this article we discussed four neurologic syndromes associated with COVID-19 that may benefit from interdisciplinary rehabilitation strategies. There is limited data on outcomes of rehabilitation in these COVID-19-associated conditions, but using the non-COVID neurological syndromes as models is the first step toward more effective treatment of these patients.

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Cognitive Complications of COVID-19 Infection

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ABSTRACT

SARS-CoV-2 is associated with a post-infectious neurocognitive syndrome characterized by fatigue and deficits in attention, memory, and executive function. As screening cognitive testing generally remains normal, the pathophysiologic basis of these symptoms remains controversial and there is no standardized treatment paradigm. We present a clinical case demonstrative of typical neurocognitive sequelae of SARS-CoV-2 infection, highlighting medical and social factors that may have contributed to the severity of symptoms. We discuss the pathophysiologic evidence for cognitive “brain fog” following COVID-19 infection as well as lifestyle changes and rehabilitation strategies that may improve recovery. As the benefits of pharmacologic therapy remain unproven, we close with a brief discussion of medication options that might be appropriate targets for future clinical trials in the context of rehabilitative treatment.

KEYWORDS: Long COVID, PASC, brain fog, dysexecutive syndrome

CLINICAL CASE PRESENTATION

A 56-year-old woman with no significant medical history was infected by SARS-CoV-2 in October 2020, prior to the availability of commercial vaccinations. She experienced mild respiratory symptoms with loss of her sense of taste and smell, and then developed fatigue, difficulty concentrating, severe dyspnea on exertion, and exertional tachycardia. When these symptoms persisted for five months, she sought multidisciplinary care from infectious diseases, neurology, and cardiology specialists.

She had remained out of work because fatigue and cognitive symptoms limited her abilities and she was unable to meet the requirements of her demanding clerical job. She felt a general fogginess of mind, accompanied by forgetting details, trouble concentrating, and a remarkable difficulty with multitasking, which was well below her baseline. She also slept for long periods during the day but had difficulty remaining asleep at night and overall had poor sleep quality. She was unable to return to her regular exercise regimen due to her fatigue and exertional symptoms.

Her initial neurological evaluation revealed a perfect score (30/30) on the Mini-Mental Status Examination, a normal neurological examination without neglect or focal cognitive symptoms, and a normal electroencephalogram and magnetic resonance image (MRI) of the brain. She was treated conservatively, with recommendations to engage in intellectually stimulating activities and practice sustaining attention to specific tasks (in her case, meditation and yoga).

She attempted a gradual return to work, but failed to perform as required. During a particularly alarming episode, she could not recall the details of a conversation on the previous day, even with cueing. Due to her residual cognitive impairments six months following infection, she was referred for a formal neuropsychological evaluation.

In contrast to her normal performance on cognitive screening tests, her deficits on a neuropsychological test battery were striking. She had mild to moderate impairments in multiple domains, including attention, processing speed, executive control, fine motor dexterity, learning, and memory. However, these deficits were present only in a subset of tests of executive control within each cognitive domain. Notably, embedded measures of mood and effort showed no evidence of depression or intentional underperformance. She was diagnosed with a dysexecutive pattern of cognitive impairment and met criteria for mild neurocognitive disorder.

A trial of donepezil subjectively improved the cognitive symptoms, but without clear objective benefit. Her cardiac evaluation showed evidence of myocarditis and she underwent cardiac rehabilitation with a gradual return to her previous exercise tolerance and frequency. Ten months after her infection, she returned to work part-time but was able to perform at only 20% of her previous productivity level. She continued to work on sustaining attention to single tasks and avoided multitasking in order to complete her work duties.

Repeat neuropsychological testing a year later demonstrated improvements in executive aspects of attention and cognitive flexibility, but her memory and semantic fluency were unchanged. Seventeen months following her initial infection, she continued to meet neuropsychological criteria for mild neurocognitive disorder. She did not regain her sense of smell or taste. Her overall cognitive profile was consistent with the emerging literature on the Long COVID neurocognitive syndrome.
COGNITIVE SYMPTOMS FOLLOWING SARS-COV-2 INFECTION

The post-acute sequelae of SARS-CoV-2 infection (PASC) are a growing health crisis, estimated to currently impact 110,000 Rhode Island residents.1 PASC is an umbrella term for multisystem involvement (pulmonary, cardiac, musculoskeletal, etc.) that persists longer than 4 weeks after the acute COVID-19 infection. This article focuses specifically on the cognitive PASC that cannot be readily explained by acute events during infection, such as global hypoxic injury or stroke.

Our patient provides a typical example of the neurocognitive syndrome associated with SARS-CoV-2 infection, and case series have consistently highlighted a range of deficits in executive function.2,3 Here, executive function refers to the cognitive processes (e.g., organization and planning) that control our more basic cognitive functions.4 Executive control is less important for routine or memorized behaviors but is critical when we are confronted with novel tasks, unfamiliar environments, or conflicting rules. These situations arise routinely in day-to-day human life.

Given the major influence of executive function over other cognitive domains, it follows that dysexecutive impairments can cause difficulties in attention, concentration, processing of new information, task selection and monitoring, and manipulation of working memory.4 Multi-tasking is especially impaired, because the difficulty of each simultaneously performed task is effectively multiplied.5

Executive dysfunction is experienced uniquely by each patient. Some may present with a specific concern such as forgetfulness or trouble focusing and others with subtle global dysfunction that causes them to feel foggy or slow. The primary symptom is likely related to the cognitive domain that is most stressed in the patient’s life. Function outside the home is likely to be more impaired than at home, where habits and routines can compensate.

Regarding the incidence of cognitive PASC, high quality prospective data are limited because many large studies only asked about fatigue, did not control for acute stroke or hypoxia, or had study design biases. Acknowledging these challenges, current estimates range from 7% to 54%,6 with individual cohort rates as high as 81%.7,8

There are some studies of cohorts similar to our patient. A longitudinal prospective study5 followed subjects who had premorbid cognitive, MRI, and EEG data, and excluded patients who were hospitalized, required oxygen, or developed new MRI lesions. Patients who became SARS-CoV-2 seropositive averaged a 2-point decline in their Montreal Cognitive Assessment (MOCA, maximum score 30) from baseline, and 21% experienced a loss of 4+ points, which met the criterion for measurable cognitive decline in this cohort.

Critically ill patients have higher rates of cognitive dysfunction following COVID-19, but this is proportional to their higher rates of stroke and other medical complications.10 Some propose that critically ill patients may suffer from a concurrent post-ICU syndrome that is not unique to COVID-19,11 creating a multifactorial cognitive disorder with complicated rehabilitation needs.

Unfortunately, the benefit of vaccination in preventing PASC is limited. In one review of VA medical records, vaccination was associated with only a 15% relative risk reduction of developing PASC following breakthrough infection, though sub-analysis verified protective benefit specifically against cognitive dysfunction.10 Thus, even with widespread vaccination, a significant clinical population will experience cognitive changes following COVID-19 infection.

It remains to be seen whether emerging COVID-19 variants will be associated with similar rates of cognitive dysfunction. In population-level studies, the Omicron variant had half the incidence of PASC compared to the Delta variant,12 but available studies do not distinguish cases on the basis of variant. Similarly, the link between neurological and other systemic manifestations of PASC is not well studied.

PATHOPHYSIOLOGY OF COGNITIVE SYMPTOMS

Even mild SARS-CoV-2 infection is associated with up to a 20% risk of developing dysexecutive cognitive impairment.2,9 This is seen across multiple case series with varying disease severity,11,12 cognitive assessment tools,6 various cultural settings,6,9,15,16 and age groups including the asymptomatic elderly.17 We argue that it represents a distinct clinical entity with a physiologic basis that is under investigation.

There are ongoing efforts to explain how SARS-CoV-2 infection results in prolonged cognitive dysfunction. An inflammatory process is suspected,18 whether from direct viral activity in the brain19,20 or through a parainfectious process. The inflammation may be more prominent in limbic and frontomedial regions of the brain, as they are closer to the olfactory epithelium.21–23 The pathophysiologic process involves endothelial disruption,24 microglial activation,19 neurotransmitter depletion,25 and microvascular compromise.26 This process appears to cause leukoencephalopathy27 and accelerated focal and global cortical atrophy,21 with resultant network dysfunction and cognitive changes.

No studies provide strong evidence for using anti-viral or anti-inflammatory medications to prevent or treat cognitive PASC. As the NIH COVID-19 Treatment Guidelines Panel does not recommend steroid therapy for patients that do not require oxygen support,28 any retrospective study would likely be confounded by differences in disease severity or degree of hypoxia. This remains an avenue for further clinical investigation.

CLINICAL MANAGEMENT OF COGNITIVE PASC

As there is no established treatment regimen, the management of cognitive symptoms following SARS-CoV-2
infection focuses on supportive care and the identification and treatment of other confounding medical factors. A high index of suspicion is necessary to recognize the dysexecutive pattern typical for neurocognitive PASC. This syndrome may present as a specific cognitive concern, as generalized fogginess or trouble with concentration or memory, or as difficulty at work or in community activities. Generally, elderly people and those with premorbid intellectual or cognitive disability are disproportionately affected.

Inappropriate behavior or violations of social norms should raise concern for alternative frontal lobe pathology. Similarly, a patient showing progressive declines over time should raise concern for an underlying degenerative process versus another comorbid risk factor for cognitive impairment. It is also possible that cognitive PASC could be superimposed on premorbid neurological conditions.

Patients should undergo a thorough screening for alternative causes of cognitive dysfunction, including a basic metabolic panel, complete blood count, vitamin B-12 and folic acid levels, thyroid function tests, a routine non-contrasted MRI of the brain, and other tests guided by the clinical picture. A relatively normal brain MRI is expected and structural lesions should prompt pursuit of alternative diagnoses such as ischemic stroke or frontal lobe tumor. If leukoaraisis or ischemic white matter disease is detected, then aggressive control of microvascular risk factors should be initiated, with screening for hypertension, diabetes, and hyperlipidemia. Any comorbid mood or sleep disorders [e.g., depression or sleep apnea] that may contribute to poor cognitive performance should also be addressed.

If the initial diagnostic workup is reassuring, we recommend a period of symptom monitoring with a patient-directed cognitive rehabilitation regimen. Lifestyle changes for improved brain health include intellectually stimulating activities, community engagement, good sleep quality, smoking cessation, avoidance of mind-altering substances such as marijuana and alcohol, regular exercise, and a healthy diet.

A core challenge in the dysexecutive syndrome is that difficulties with attention and working memory often leads to a marked loss of the ability to multitask. To compensate for this, we recommend activities that allow focusing on a single task or thought process for progressively longer periods of time. In this manner, one can complete a series of tasks efficiently, allowing progression through a list and achieving a level of productivity that is similar to multitasking. In our case, yoga and meditation were recommended; however, one may find similar benefits in other exercises or outdoor activities, a game or puzzle, an art or crafting activity, reading a book, or enjoying music. In contrast, television or video media can impair sustained attention due to frequent scene changes and distracting elements. This approach is similar to the strategies for improving executive functioning following traumatic brain injury.

There have been mixed reports regarding the potential for COVID-19 vaccination after acute infection to improve PASC symptoms. Vaccination appears to be safe and does not worsen symptoms or quality of life. Given the possibility of reinfection [and further cognitive insults] and the modest but measurable protection that vaccination offers, we recommend full vaccination with booster doses following CDC guidelines if the patient has not undergone it.

Regarding medical management of PASC, there are no available clinical trials to support the use of any particular pharmacotherapy. In the acute phase, selected sigma-1 receptor modulating antidepressants [e.g., fluvoxamine] have been postulated to have a neuroprotective role, but this has not translated into a treatment recommendation for acute or post-acute care. Case reports, such as in this article, do not demonstrate clear and consistent benefits, and the side effects of cognitive stimulants can be significant.

Further pharmacologic insights might be gleaned from a related condition that is often compared to the post-COVID brain fog, that of chemotherapy-induced cognitive impairment. The effects of various classes of cognitive enhancers have been reviewed in this context. In general, results were promising in small and carefully selected patient cohorts, often with preexisting cognitive difficulties. Clinical trials are ongoing, and no general treatment recommendation can be made at this time.

Given the lack of high-quality clinical data and the concern for side effects and adverse cognitive changes, we do not recommend routine pharmacotherapy in the management of cognitive PASC.

In the absence of alternative pathology, we recommend symptom monitoring, lifestyle optimization, and attention training for a period of six months. If symptoms persist at that time, we obtain formal neuropsychological testing for a baseline measure of cognition; determine the likelihood of alternative pathologies; and select targeted interventions with the assistance of occupational or speech and language therapists. A formal neurological evaluation should be considered for any patient who does not present with typical symptoms, has ongoing progression of symptoms following the acute infection, or has focal examination or imaging findings.

CONCLUSION

Mild SARS-CoV-2 infection is associated with a prolonged neurocognitive syndrome of impaired executive function in as many as 20% of cases. The chief complaint and major symptoms expressed may vary between patients as a function of their premorbid status and lifestyle. There is no recommended pharmacotherapy at this time, and treatment focuses on establishing an individualized cognitive rehabilitation regimen and excluding or treating other comorbid conditions that may impair cognition.
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22. Chuang-Kuo Wu, MD, PhD, Department of Neurology, Brown University, Providence, Rhode Island. Comments: The views expressed herein are those of the authors and do not necessarily reflect the views of Brown University or its affiliated hospitals.

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Long-term Orthopedic Manifestations of COVID-19: Heterotopic Ossification and Digital Necrosis

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ABSTRACT
Despite its classification as an atypical pneumonia, COVID-19 is a disease that is capable of inflicting damage beyond the respiratory system. The wide range of musculoskeletal complications secondary to acute COVID-19 are a significant source of morbidity in hospitalized patients. We present the case of a 23-year-old woman with severe COVID-19 who required intubation and had a prolonged hospital course that was complicated by partial-thickness necrosis of her fingers and heterotopic ossification of the distal thigh. We review current treatments for these orthopedic conditions in the setting of SARS-CoV-2 infection as well as highlight areas for future research. Additionally, we discuss the subacute musculoskeletal complications of COVID-19, which are among the most common long-term manifestations of the disease and are increasingly important for a growing number of COVID-19 survivors.

KEYWORDS: COVID-19; orthopedic; heterotopic ossification; digital necrosis

INTRODUCTION
In late 2019, the first cases of the novel coronavirus disease 2019 [COVID-19] caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. Since then, the disease has become a worldwide pandemic resulting in hundreds of millions of cases and more than 6 million deaths. Although initial attention focused primarily on the respiratory ramifications of the disease, COVID-19 is now recognized as a multi-system disease that can cause potentially devastating complications and long-term dysfunction throughout the body.

A variety of musculoskeletal complications related to both acute and post-acute sequelae of COVID-19 [PASC, also known as “Long COVID”] have been reported. These complications may in part be explained by the presence of angiotensin-converting enzyme 2 [ACE-2], the virus’s major entry receptor, on skeletal muscle, synovial tissue, and the endothelium of small vessels. Additionally, the widespread and prolonged inflammatory response as well as a prothrombotic state triggered by SARS-CoV-2 infection probably plays a role. We present a patient with severe COVID-19 who required intensive care unit [ICU] admission and mechanical ventilation. Her case was further complicated by heterotopic ossification of the distal thigh and digital necrosis. Additionally, we review other frequently reported musculoskeletal complications of COVID-19 illness and treatment both in the acute and subacute settings.

CASE REPORT
A 23-year-old woman [unvaccinated against SARS-CoV-2] was admitted with shortness of breath and weakness due to COVID-19, after a normal vaginal delivery five days previously. A computed tomography angiogram [CTA] of her chest demonstrated pneumomediastinum, a segmental filling defect in the left lower pulmonary artery, and diffuse ground-glass opacities consistent with COVID-19 pneumonia. She was admitted to the intensive care unit and intubated for persistent respiratory distress. Her 81-day hospital course was complicated by refractory hypoxemia treated with venovenous extracorporeal membrane oxygenation [VV ECMO], pneumomediastinum, subsegmental pulmonary emboli, and disseminated intravascular coagulation managed with cryoprecipitate transfusions.

This patient also experienced orthopedic complications, and on hospital day 38 the Orthopedic Hand Service was consulted for partial thickness necrosis and dry eschars of the nail and dorsal fingertips distal to the distal interphalangeal joint [DIP] of the right index, middle, and ring fingers [Figure 1a]. No acute findings were evident on plain radiographs [Figures 2a-c]. The physical exam was limited due to the patient’s intubated status. She had signals via Doppler ultrasound at the radial and ulnar arteries as well as her deep and superficial palmar arches. Her partial thickness digital necrosis was managed conservatively with refactory hypoxemia treated with venovenous extracorporeal membrane oxygenation [VV ECMO], pneumomediastinum, subsegmental pulmonary emboli, and disseminated intravascular coagulation managed with cryoprecipitate transfusions.

She was evaluated and followed by occupational therapy for upper extremity strength and range of motion [ROM] training and activities of daily living [ADL] training throughout her hospital course.
Several weeks after the appearance of her partial thickness digital necrosis, the Orthopedic Service was consulted for atraumatic left medial knee pain. She had a palpable, firm, non-fluctuant mass at the left distal medial thigh and both active and passive motion of the left knee were limited by pain. Radiographs and computed tomography (CT) scans demonstrated heterotopic ossification of the left vastus medialis (Figures 3a,b, Figures 4a-c). She was treated with nonsteroidal anti-inflammatories for pain control and physical therapy. She was seen by physical therapy throughout her hospital course for strength and range of motion (ROM) training as well as gait training, with nearly full resolution of her knee ROM. She was discharged to an acute rehabilitation center to facilitate recovery of her strength, flexibility, and functional independence. At two months after discharge, she had regained lower extremity strength and ROM, was able to ambulate with assisted devices, and had achieved independence with functional mobility.

**DISCUSSION**

Early in the pandemic, COVID-19 was characterized as an atypical pneumonia, but it is better understood as a multi-system disease, as exemplified by our case of a 23-year-old woman with severe COVID-19 whose prolonged hospital course was complicated by heterotopic ossification and digital necrosis.

Endothelial dysfunction, inflammatory cytokine release, and hypoxia trigger decreased production and increased consumption of naturally occurring anticoagulants during severe
viral infection. In COVID-19, direct endothelial injury from the SARS-CoV-2 virus via the ACE2 receptor may further exacerbate the coagulopathy. The prothrombotic state can result in macrovascular as well as microvascular complications, such as the partial thickness digital necrosis seen in our patient. Of note, digital necrosis is also well-described in patients requiring vasopressors and ICU-level care. Thus, the exact etiology of acral necrosis in the setting of COVID-19 is likely multi-factorial and incompletely understood. Purpura, the cutaneous pattern that precedes digital gangrene in many of the reported cases, is characteristic of an occlusive micro-thrombotic process. The preservation of major peripheral pulses in many cases also suggests a microvascular etiology. Freeman et al analyzed six acral retiform purpura or necrotic lesions associated with COVID-19. The histopathology demonstrated non-inflammatory to pauci-inflammatory thrombi, leading the authors to conclude that acral necrosis is a cutaneous manifestation of the hypercoagulable state in COVID-19 patients. However, poor responses to anticoagulation regimens have been reported in several cases of acral ischemia associated with COVID-19, prompting hypotheses that other processes such as neutrophil extracellular traps (NETs) or cold-sensitive antibody/immunoglobulin responses to the virus may play a role in the pathology.

No standardized protocol exists for treatment for COVID-19-associated digital necrosis. The most common treatment reported in the literature is early and aggressive anticoagulation. Further investigation is needed to determine if targeted immunotherapy or pharmaceutical agents dissolving NETs prove effective in treating digital ischemia unresponsive to anti-coagulation therapy. In the majority of reported digital necrosis cases, patients responded to conservative management, including wound care and anticoagulation, or they died from other effects of COVID-19; however, Morales-Perez et al presented a case of surgical reconstruction of a necrotic thumb as well as a review of digital reconstruction in the setting of microvascular disease.

In addition to digital necrosis, patients with severe COVID-19 are also at risk for heterotopic ossification (HO), a musculoskeletal complication characterized by ectopic formation of bone in soft tissues and around joints. The exact mechanism of traumatic HO remains unclear. It is thought to involve the differentiation of perivascular mesenchymal cells into osteoblasts when exposed to proinflammatory cytokines in the setting of altered local tissue factors, such as oxygen tension and pH. In addition to the global inflammation experienced by COVID-19 patients, those requiring intubation are subject to prolonged
immobilization, another known risk factor for development of HO.\textsuperscript{19,22} In fact, the reported cases of HO associated with COVID-19 have occurred exclusively in individuals who required mechanical ventilation.\textsuperscript{20-22} In the largest series on the topic, Stoira et al retrospectively analyzed CT imaging of 52 intubated COVID-19 patients and found evidence of HO in ten (19%).\textsuperscript{20} Symptomatic HO presents most commonly as pain or loss of motion at a joint and has been reported around the hip, shoulder, or knee of COVID-19 patients requiring ICU level of care.\textsuperscript{20-22} The diagnosis can be confirmed with radiographs; however, they have limited sensitivity early in the process.\textsuperscript{17} Given the limited literature on HO with COVID-19, treatment options are based on those utilized for HO secondary to neurologic insult or local trauma. NSAIDs, bisphosphonates, and radiation therapy are effective strategies to prevent HO in certain settings but no pharmaceutical treatment exists to address HO after it has formed.\textsuperscript{17,18} NSAIDs can be utilized for prophylaxis and pain relief, but surgical removal remains the standard treatment when there is functional impairment and lack of improvement with conservative management including pain control and physical therapy.\textsuperscript{17} The role of physical therapy in treating HO is a controversial topic. Historically, HO was considered a contraindication to range of motion exercises, based on the formation of ectopic bone in animal models subjected to aggressive stretching.\textsuperscript{25,26} However, more recent research suggests that passive stretching may help preserve joint range of motion in patients with HO.\textsuperscript{19,27} The optimal timing and types of physical therapy interventions have yet to be determined.

The musculoskeletal complications of COVID-19 are not limited to the acute effects of the disease and its treatment. In a long-term study of 285 patients, Karray et al found that 40% of survivors had at least one musculoskeletal symptom six months post-infection, most commonly fatigue, joint pain, or myalgia.\textsuperscript{4} A meta-analysis of persistent post-acute sequelae in more than 250,000 survivors found similar rates of muscle weakness.\textsuperscript{28} Although critical illness myopathy is a well-documented consequence of ICU treatment for COVID-19 and other diseases, myopathic changes have also been documented in patients with mild COVID-19 infection, suggesting a different etiology in some cases.\textsuperscript{29,30} Proposed mechanisms for post-acute muscle weakness include viral infiltration into skeletal muscle or muscle damage secondary to an aberrant immune response.\textsuperscript{31} Physical activity has proven a powerful tool for preventing and improving myopathy associated with long-term COVID-19.\textsuperscript{1,31} Rehabilitation should begin as soon as sedation and clinical stability allow; previous studies have demonstrated the feasibility and benefits of ambulation in ICU patients.\textsuperscript{32} Post-hospitalization, recovering patients should partake in exercise that balances strength and flexibility to improve their gait as well as regain muscle mass.\textsuperscript{1} Exercise programs proven effective in restoring function in randomized controlled trials involving SARS-CoV-1 survivors could serve as helpful templates for current efforts to develop rehabilitation protocols.\textsuperscript{33} Recent studies have also explored the role of neuromuscular electrical stimulation and vitamin D supplementation in preserving and recovering muscle function, although further research is needed to determine the effectiveness of these modalities.\textsuperscript{34,35}

Despite increasing availability of vaccines and treatments for COVID-19, hundreds of thousands of new infections occur daily.\textsuperscript{2} Questions about the pathogenesis and optimal treatment for COVID-19-associated musculoskeletal conditions, especially long-term effects, require continued investigation. Increased understanding of the orthopedic manifestations of the disease is critical to improving care for patients and minimizing the healthcare burden.

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Delta-9-tetrahydrocannabinol (D9-THC) is the driving cannabinoid within cannabis that produces its psychoactive effects. However, the plant itself contains over 400 individual chemicals, many with unique pharmacological properties. Further complicating the cannabis market, chemical modifications have been identified to convert naturally derived cannabinoids to alternative cannabinoids and the collection of synthetic cannabinoids, manmade chemicals designed to act at cannabinoid receptors, continues to grow. Recent years have seen a rise in popularity of these alternative cannabinoids, and this trend is likely to continue with the continuing legalization of recreational cannabis throughout the United States. It is vital for medical providers to not only be aware of the wide range of available cannabinoid products, but to be conscious of their differing properties. The current work aims to identify commonly used alternative cannabinoids, examine their complicated legality, and summarize the available literature regarding their clinical effects.

KEYWORDS: cannabis, alternative cannabinoids, cannabis regulation

INTRODUCTION
With the passing of the Rhode Island Cannabis Act, the state became the 19th across the country to legalize recreational cannabis. The plant has been cultivated for millennia for materials and oil but has been restricted over the past century due to its psychoactive effects. Its prohibition unfortunately hindered clinical research regarding its properties, including medical benefits and safety effects.

To most, cannabis is synonymous with delta-9-tetrahydrocannabinol (Δ9-THC). Δ9-THC is the driving cannabinoid which gives users its psychoactive effects. More recently, cannabidiol (CBD) has received media attention for potential anti-inflammatory, immune-boosting, anxiolytic, and antiepileptic health effects, with a lack of subsequent intoxication. Most cannabis-related medical literature to date has been focused on these two cannabinoids, but the cannabis plant itself contains over 400 different chemicals, with 18 of these shown to have pharmacological and toxicological properties. The effect of differing cannabinoid combinations, ratios, and how isolating specific cannabinoids compared to whole plant use impacts clinical effects is understudied. Some studies suggest that differing concentrations and ratios of THC:CBD result in divergent subjective effects. For example, at some concentrations, CBD has been reported to dampen psychoactive effects of THC, but at other ratios paradoxically amplify THC effects. These limited studies reveal we have only started to uncover the complexity of cannabinoid effects and interactions.

The discovery of the endogenous cannabinoid system shifted pharmacologic focus in an attempt to separate the psychoactive effects from certain medical benefits. Limited research led to the discovery of the endogenous cannabinoid system, where endocannabinoid ligands (e.g., 2-arachidonoyl glycerol and anandamide) act on both CB1 and CB2 receptors throughout the body. CB1 receptors are present primarily in presynaptic neurons and help dictate neurotransmitter release while CB2 receptors are typically found outside the CNS and are primarily expressed on immune cells. The discovery of these receptors and their effects has played a role in the rise of synthetic cannabinoids, manmade chemicals designed to act at the cannabinoid receptors. This led to the development of Marinol, a synthetic THC derivative, FDA-approved as an antiemetic agent for chemotherapy patients. Additionally, Rimonabant, a CB1 antagonist to combat obesity, was briefly approved in Europe, but the drug was eventually discontinued due to psychiatric side effects.

Each cannabinoid’s differing psychoactive profile is dictated by its specific chemical structure. Chemical modifications have been identified to convert naturally derived cannabinoids to alternative cannabinoids. As an example, THC-O, a potent alternative cannabinoid, can be synthesized from Δ9-THC with a similar laboratory technique that forms aspirin (acetylsalicylic acid) from willow bark (salicylic acid). Aging of cannabinoids may also naturally
lead to decarboxylation of these compounds. Even the heat from smoking itself has been shown to alter chemical bonds, and studies assessing the volatilization of cannabinoids have shown that CBD is partially converted to THC during smoking.

Additional confusion stems from the colloquial distinction between two available cannabis products: *Cannabis sativa* and *Cannabis indica*. It is typical for cannabis dispensaries to recommend the latter for anxiety as there is a preconceived notion that *Cannabis indica* is more relaxing than the uplifting *sativa* species. However, research has yet to validate this distinction, and it is important for providers to be aware that both can contain drastic ranges of THC and CBD. The degree of interbreeding and hybridization in recent decades has also made it difficult to adequately identify a cannabis plant’s species and subsequent proposed psychoactive properties based solely off its physical structures such as leaf morphology or branching.

As more is learned regarding each cannabinoid’s specific properties, there is inevitably going to be a proliferation of products utilizing alternative cannabinoids. CBD has been the face of the alternative cannabinoid world due to its availability, but specialized breeding is currently increasing the concentrations of other minor cannabinoids. Their popularity has drawn attention in the media and there has already been a shift toward commercial use, particularly within the beauty and wellness sectors. Because of this, it is important for physicians and other healthcare providers to be conscious of the differing products available and their wide range of cannabinoid profiles. The present work aims to provide a review on existing literature regarding common cannabinoids, their legality, and the clinical response to their use. [See Figure 1.]

**DELT A-9 (Δ9-THC)**

The everchanging recreational and medical legality of cannabis within the United States typically refers to Δ9-THC. The compound itself is directly extracted from the cannabis plant, in contrast to most alternative cannabinoids which are chemically modified. As it is the most abundant psychoactive cannabinoid, most research regarding cannabis directly investigates its properties. Both the nausea suppression in patients receiving chemotherapy and the pain-reducing benefits in those with multiple sclerosis have been shown to be driven by this specific isomer.

Like most psychoactive drugs, the effects of Δ9-THC are dose dependent. The concentrations of cannabis products are typically described by the amount of Δ9-THC per dry weight. The average cannabis potency today is estimated to be ~20%, meaning that a gram of cannabis is 200mg of Δ9-THC. Breeding and specialized genetics have led to drastic increases in percent THC within lines of the cannabis plant. Since 1970, these concentrations have increased an average of 0.29% per year. In nearly all previous cannabis studies looking at analgesia, Δ9-THC concentrations were lower than 10%, which will need to be accounted for as medicinal research moves forward and potencies continue to increase.

Δ9-THC is primarily hepatically metabolized through the cytochrome P450 system, but alternative extrahepatic metabolism has been shown in other organs through hydroxylation pathways. Based off previous clinical studies which utilized receptor antagonists, it has been shown that the psychoactive effects of Δ9-THC are largely driven through the forementioned CB1 receptor, leading to adenylyl cyclase inhibition. The cannabinoid has been shown to have a wide range of bioavailability depending on the route of administration, typically inhalation of cannabis smoke or in an edible form. In addition to these routes, there has been an increase in popularity over recent years of vaporizing high potency Δ9-THC oil. This form gained notoriety in 2019 due to EVALI (E-cigarette or Vaping Use-Associated Lung Disease). It has been hypothesized that unregulated oil compounds contained Vitamin E at this time, leading to an aggressive inflammatory response within the lungs. Similar to tobacco products, the long-term effects of vaping are yet to be identified.

The majority of drug tests in the United States assess for

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**Figure 1.** A: Delta-9-tetrahydrocannabinol (Δ9-THC), B: Cannabidiol (CBD), C: Delta-8-tetrahydrocannabinol (Δ8-THC), D: Delta-10-tetrahydrocannabinol (Δ10-THC), E: Tetrahydrocannabinol (THC-P), F: O-acetyl-Δ9-THC (THC-O), G: Cannabinol (CBN)
cannabis by testing for Δ9-THC metabolites, but there is overlap with other cannabinoids. Δ9-THC, along with all other reported cannabinoids, is highly lipophilic, leading to its storage within adipose tissue in the body. This leads to delayed excretion, particularly when compared to other commonly used drugs, as heavy users can test positive in urine testing up to 30 days from last use.

CBD (CANNABIDIOL)
Cannabidiol has become popular in recent years as a cannabinoid with minimal to no psychoactive effects. There has been a large uptick in CBD-labeled health products in recent years due to its proposed benefits and the global market of CBD is estimated to reach US $47 billion by 2028. While it is widely available, it is not federally legalized and is instead dictated by individual states. That said, even the strictest states have avenues to obtain it legally.

Commonly taken orally or as a topical cream, CBD has been shown to have both analgesic and anti-inflammatory effects by acting as a cyclooxygenase and lipoxygenase inhibitor. It has low affinity for the forementioned CB1 and CB2 receptors, but rather has been shown to work primarily through GPR55, a receptor expressed primarily in the caudate nucleus and putamen. Like other cannabinoids, CBD is primarily heptatically metabolized. It has been recommended that patients receiving CBD have their bilirubin and transaminase levels monitored before and during treatment to assess for hepatotoxicity.

While CBD can be found in many stores, the FDA has only approved its use through Epidolex. The drug is a purified form of CBD for the treatment of seizures in patients with Lennox-Gastaut or Dravet syndrome. Studies regarding this medication have shown side effects including diarrhea, decreased appetite, and poor sleep quality. Currently, clinical trials are investigating the use of CBD in other disorders, such as anxiety, chronic pain, and neurodegenerative diseases.

A CBD specific drug test exists, but it is not typically performed due to the cannabinoid’s lack of psychoactive properties. The compound itself should not lead to a positive THC drug screen, but many products have been shown to contain small amounts of THC, even if not labeled this way.

DELTA-8 (Δ8-THC)
Delta-8 is a natural yet historically ignored derivative of cannabis. While it has seen an increase in use in recent years, the ability to synthesize the isomer from CBD has been known for over 80 years. It is nearly identical to Δ9-THC, only differing in the location of a single carbon double bond, which is enough to drive its divergent psychoactive properties. The alternative cannabinoid has been shown in studies to have a stronger affinity for CB receptors than Δ9-THC. However, Δ8-THC is roughly half as potent as Δ9-THC and some sources state that the cannabinoid has greater appetite stimulating effects and less anxiety. Based on limited data, the reported side effect profile of Δ8-THC is similar to Δ9-THC. It can be taken orally but is typically smoked like common strains of cannabis.

The slight alteration in its structure has led to a federal debate and laxity in its regulations, leading to its rise in popularity in recent years. In September of 2021, the DEA deemed that cannabinoids extracted from the cannabis plant with Δ9-THC concentrations under 0.3% by dry weight meet the definition of hemp and thus are not controlled substances. Many have argued that this statement protects Δ8-THC as it is a cannabinoid which doesn’t contain Δ9-THC. Even more confusion stems from the fact that the majority of available Δ8-THC in the country should be deemed synthetic, which would seemingly exclude it from the DEA’s stance. While Δ8-THC can naturally be extracted from the cannabis plant, it is found in such small quantities that the process isn’t economical. Because of this, the most available product is formed through a conversion process from CBD with the use of acids, typically hydrochloric or sulfuric acid. This process can lead to impurities and small amounts of other cannabinoids, such as Δ10-THC. Because of this, it is important for clinicians to recognize that available products are often not pure Δ8-THC, even if advertised this way. Recent years have seen more states become stringent against this cannabinoid. Prior to the Rhode Island Cannabis Act, the state had made note that it deems Δ8 and any other isomer to be treated the same as a Schedule 1 Controlled Substance. Alternative cannabinoids were not specifically addressed in this recent passed law. As of now, the cannabinoid is regulated to at least some degree in 19 other states.

From a clinical standpoint, common immunoassays cannot note the difference between Δ8-THC and Δ9-THC so patients will test positive for THC after using either isomer. If there is any necessity to delineate, chromatographic methods can be used. There has been little research looking into the pharmacokinetic profile of Δ8-THC, particularly from an oral route. However, based on limited data, its distribution around the body unsurprisingly appears to be like that of Δ9-THC.

DELTA-10 (Δ10-THC)
Like Δ8-THC, Δ10-THC is also an isomer solely differing in the location of its double carbon bond. The cannabinoid isn’t typically found as a natural component of cannabis but has been known since the 1980s when it was first synthesized. While it can be synthesized directly from Δ9-THC, it is typically formed as an impurity when Δ8-THC is synthesized from CBD.
It has been shown to bind and utilize the same CB₁ and CB₂ cannabinoid receptors throughout the body. There is little data regarding this alternative cannabinoid, but most reports deem it to be less potent than Δ⁹-THC. While there have been no clinical trials directly comparing the two,¹⁰ users typically report more stimulating properties than the mellowness associated with Δ⁸-THC. Because of this, there are many products that contain a mix of both Δ⁸-THC and Δ₁₀-THC. Like other alternative cannabinoids, Δ₁₀-THC will lead to a positive THC immunoassay drug test in patients.

**THC-P (TETRAHYDROCANNABIPHOROL)**

The highest potency cannabinoid naturally found in both hemp and cannabis, albeit in small concentrations, is THC-P. It has been reported to have potencies up to 33 times that of Δ⁹-THC. Its differences are hypothesized to be secondary to additional carbon atoms within its alkyl side chain.²¹ While most cannabinoids have a pentyl side chain, THC-P has two additional carbon atoms. It has the highest binding affinity to CB₁ receptors of any naturally occurring cannabinoid, but newer synthetic cannabinoids are actively being created with reported higher potencies. Minimal research performed in mice has indicated similar cannabimimetic activity to Δ⁹-THC, inducing analgesia, hypomobility and decreased temperature.²¹ THC-P breakdown within the body leads to THC-COOH, the same metabolite formed by Δ⁹-THC. Because of this, users of THC-P would have a positive immunoassay standard THC drug screen.

The heptyl homologue of CBD, Cannabidiphorol, was identified in the same Italian study performed in 2019.²² Little is known regarding its clinical properties or pharmacokinetics. Future research is necessary to examine possible increased anti-inflammatory properties secondary to its presumed higher binding affinity.

**THC-O (O-ACETYL-Δ⁹-THC)**

THC-O, also referred to as THC-O-acetate, is an alternative cannabinoid that is not naturally found within the cannabis plant but has been gaining popularity over recent years. It is available in vape cartridges, edibles, and tinctures. Reports have noted a potency up to three times that of Δ⁹-THC.²³ In contrast to THC-P, its potency doesn’t stem from extra carbon atoms in its alkyl chain. Rather, an acetate group within the molecule significantly increases its bioavailability, furthering its psychoactive effects.

Clinically, it is the only cannabinoid to have reported pseudo-dissociative effects and in high doses patients may present like they consumed hallucinogenic drugs.²³ THC-O typically refers to the acetate ester of Δ⁹-THC, but those of Δ⁸-THC and Δ₁₀-THC have also been synthesized. It is not specifically scheduled at the federal level within the United States but falls in the same gray area of other alternative cannabinoids. There are reports of THC-O being studied as far back as 1948 during the infamous Edgewood Arsenal Experiments, where the US government was studying incapacitating agents.²⁴ As most of the information regarding THC-O stems from anecdotal reports, further scientific research needs to be performed to fully elucidate its effects and pharmacokinetics. It is not currently scheduled at the federal level within the United States.

**CANNABINOL (CBN)**

Cannabinol, the first compound to be isolated from cannabis extract, is naturally found as a degradation product from Δ⁹-THC as it oxidizes. The average cannabis plant ranges between 0.1-1.6% CBN.²⁵ Opposed to many other cannabinoids,²⁶ CBN has a higher affinity to CB₁ receptors than CB₂. Unlike the forementioned THC alternative cannabinoids, CBN does not have any double bond isomers or stereoisomers. It is not specifically scheduled in the United States, but its legality is similarly in question as it could be deemed a THC derivative.

CBN has shown initial promise as a sleep aid in patients. However, the studies performed so far have not utilized polysomnography or validated sleep questionnaires.²⁷ Concerningly, studies in zebrafish have shown teratogenic effects of CBN, leading to yolk sac anomalies, tail bending and pericardial edema.²⁵

**FUTURE ALTERNATIVE CANNABINOIDS**

The forementioned cannabinoids do not encompass all known cannabinoids throughout the world, but rather are a sample of the most studied and frequently used by the general population. Additional cannabinoids that may increase in popularity include cannabigerol and cannabichromene. Cannabigerol (CBG), found in small quantities in cannabis,²⁸ is sold as a dietary supplement. Cannabichromene (CBC), also naturally occurring, has begun to show promising results regarding anti-inflammatory properties.²⁹ Epidemiological data shows that alternative cannabinoids are typically used by young adults and have been drastically increasing in frequency in recent years. As the number of discovered and synthesized alternative cannabinoids grows and the array of cannabis products and preparations expand and become easily accessible, further research will be required to assess the effects of these new cannabinoids, including long-term and in-utero effects. It is vital for medical providers to stay up to date regarding these differing cannabinoid products in order to best evaluate, treat, and counsel patients.
References


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A 57-year-old man with a history of right pneumonectomy for squamous cell lung cancer who presented with dyspnea and hypotension, was found to have pericardial effusion complicated by cardiac tamponade, associated with pembrolizumab therapy. Pericardiocentesis could not be safely attempted due to presence of right-sided mediastinal tissue shift in the setting of previous right pneumonectomy. The patient improved significantly with surgical placement of pericardial window. Analysis of the pericardial fluid was negative for malignancy and was consistent with acute inflammation. Pembrolizumab and other immune checkpoint inhibitors are associated with cardiovascular toxicity, including pericardial effusion and in rare cases, cardiac tamponade. Treatment of cardiac tamponade in post-pneumonectomy patients may be subject to anatomical limitations precluding percutaneous pericardiocentesis and requires early recognition as well as availability of surgical intervention.

Keywords: immunotherapy-related adverse events, pembrolizumab, cardiac tamponade, post-pneumonectomy

Introduction
As immune checkpoint inhibitors (ICIs) such as pembrolizumab have become commonplace in oncology care, immunotherapy-related adverse events (irAE) in various organ systems have been described. Cardiovascular toxicity including pericardial effusion complicated by cardiac tamponade is one such immunotherapy-related adverse event.

Case Presentation
A 57-year-old man with chronic obstructive pulmonary disease, heavy tobacco use, and Stage IVB squamous cell lung cancer requiring right pneumonectomy, with metatstatic spread to left lung and left femur, currently undergoing carboplatin, paclitaxel and pembrolizumab combination chemotherapy as well as radiation therapy presented to hospital complaining of one day of chest pain and shortness of breath. The patient reported pleuritic substernal chest pain, shortness of breath, and tachypnea. He reported low-grade temperatures and chills at home over two days. He endorsed mild nausea and decreased oral intake. He denied cough, sputum production, hemoptysis, and asymmetric lower-extremity swelling.

The patient was diagnosed with stage IVB squamous cell lung cancer three years prior to presentation and underwent right-sided pneumonectomy for his primary tumor followed by adjuvant chemotherapy which was aborted due to neuropathy. Two years later a recurrence of squamous cell carcinoma was diagnosed in the left lingula and left hip. Immediately prior to presentation the patient was initiated on radiation therapy to left lingula and left hip in addition to four cycles of carboplatin, paclitaxel, and pembrolizumab combination therapy followed by weekly pembrolizumab maintenance therapy.

On admission the patient’s blood pressure was 116/53 mm Hg, heart rate was 128 beats/min, respiratory rate was 35, and oral temperature was 36.2°C. He was in moderate discomfort due to pleuritic chest pain and increased respiratory effort. Clinical examination revealed distant heart sounds without cardiac rub, and absent breath sounds on the right side. Bilateral pitting lower extremity edema was noted.

Initial laboratory and ECG results are noted in Table 1. Bilateral lower extremity dopplers were negative for deep vein thrombosis. CT angiography of the chest with pulmonary embolism protocol revealed lingular airspace disease at the site of known malignancy, circumferential pericardial effusion, and no evidence of pulmonary embolism.

Several hours after admission, the patient’s blood pressure rapidly decreased to 82/38 mmHg. The patient was noted
to have pulsus paradoxus with a decrease in cuff pressure of 15mmHg with respirophasic variation. Urgent bedside echocardiography was performed. Despite the difficulty of obtaining echocardiographic windows due to the patient’s displaced cardiac anatomy (Figure 1), the study revealed a moderate-large sized circumferential pericardial effusion with diastolic right ventricular collapse indicative of tamponade physiology (Figure 2 and 3).

The patient was initially considered for percutaneous pericardiocentesis and drain placement. However, due to the volume loss of the right lung with rightward mediastinal shift (Figure 4) there was no safe path to the pericardial space. The patient’s liver lay between all perixiphoid approaches and the pericardium.

The patient underwent surgical placement of a pericardial window without complications. Two hundred mL of pericardial fluid was drained with normalization of blood pressure and improvement of symptoms. Pericardial fluid cytology revealed acute inflammation without presence of malignant cells on smear analysis. He was discharged from the hospital four days later in stable condition. Pembrolizumab therapy was discontinued, and the patient subsequently completed a course of radiation therapy. Follow up echocardiogram five weeks after pericardial window placement revealed only trace posterior pericardial effusion and preserved left ventricular function. The patient never developed recurrence of pericardial effusion on follow-up echocardiograms or CT after discontinuation of Pembrolizumab, reducing the likelihood that pericardial effusion was secondary to radiation or malignancy. The patient passed away one year later due to progression of his squamous cell lung cancer.
DISCUSSION

Immune checkpoint inhibitors (ICI), such as nivolumab and pembrolizumab, have garnered widespread use in oncology and are commonly associated with a variety of immune-related adverse effects including colitis, pneumonitis, hepatitis and endocrinopathies. Pericardial effusions are also common in oncological care and, in lung cancer, where they may be related to pericardial metastases, chest radiation and ICI treatment immune related adverse effects. In this case, a patient with Stage IVB squamous cell lung cancer undergoing pembrolizumab therapy presented with pericardial effusion and cardiac tamponade after four cycles of treatment. Pembrolizumab, a member of the class of ICIs, is a monoclonal antibody against programmed cell death protein 1, utilized in the treatment of advanced non-small cell lung cancer.5,6 Cardiovascular complications of ICI therapy are a rare but important clinical presentation which must be promptly recognized by clinicians.

Immune checkpoint inhibitors have been reported to affect the cardiovascular system, leading to a variety of complications including pericardial effusion and cardiac tamponade, myocarditis, vasculitis and arrhythmia. Pericardial effusions are likely to be observed within four months of ICI therapy initiation.7,8 Oristrell et al described the first described case of cytology negative cardiac tamponade with pembrolizumab in 2018, which was treated with pericardiocentesis and corticosteroids.4 Atallah-Yunes et al described a case of cytology negative pericardial effusion with pembrolizumab, which was also treated with pericardiocentesis and corticosteroids.7 Pericardial fluid analysis tends to contain acute inflammatory cells and up to 20% may contain malignant cells.9,10 Although the incidence of pericardial effusion in patients receiving ICIs is unknown, the reported rate of pericardiocentesis was 0.4% suggesting that hemodynamically significant pericardial effusion is an uncommon complication of ICI therapy.3 There are 25 reported cases of pericardial effusion associated with ICIs, with at least three complicated by cardiac tamponade, since 2016.2,12

Clinical presentation for pericardial effusion complicated by tamponade includes pleuritic chest pain, dyspnea, hypotension and tachycardia followed by circulatory collapse.11 Physical examination for presence of pulsus paradoxus, a fall in a patient’s blood pressure during inspiration by greater than 10 mm Hg, provides a clinical clue to the presence of tamponade.12 Echocardiographic examination may reveal pericardial effusion, diastolic right ventricular collapse and systolic right atrial collapse.13

Pericardial effusions related to ICI use do not have an established mechanism of origin.3 Immune checkpoint inhibitors may lead to immune system activation against micrometastases within the pericardium leading to T-cell infiltration as observed on biopsy samples of endocardial tissue, a concept known as pseudoprogression.3,14 Other reports suggest an immune-mediated serositis, due to the presence of PD-1 and PD-L1 proteins on cardiomyocytes, manifest with lymphocytic predominance in tissue biopsy without evidence of malignancy.3,7,9 It is suspected that ICI driven T cell deregulation leads to production of auto-antibodies by B lymphocytes and further T cell infiltration into affected tissues creating feedback loops of immune system activation and clinically significant presentations of cardiovascular toxicity.3,4,5,11

In cancer patients, who develop pericardial effusion while receiving ICI therapy, determining the likely cause is an essential component of prognosis and treatment. Malignancy and radiation therapy can be directly associated with pericardial effusion.1 Radiation therapy has been largely associated with delayed pericardial manifestations, with most cases of pericardial effusion reported within 12 months of therapy completion.1,17

Guidelines from The American Society of Clinical Oncology recommend cautious continuation of checkpoint inhibitor therapy for most mild (Grade 1) organ system toxicities. Grade 4 immune related cardiovascular toxicities (such as cardiac tamponade) with severe decompensation call for discontinuation of ICI therapy and treatment with high-dose corticosteroids [1-2mg/kg of prednisone].18 It should be noted that most reported cases avoided corticosteroids opting for instead for temporary or permanent ICI therapy discontinuation only.2,16 Prognosis likely depends on the severity of cardiovascular toxicity, functional status and cancer stage. Survival at 600 days was reported as 29% in patients with pericardial effusion associated with ICI therapy.3

The patient’s history of pneumonectomy and alteration of normal anatomy due to right-sided and superior displacement of the patient’s intrathoracic and intrabdominal contents prevented the use of percutaneous pericardiocentesis and drain placement. The patient required surgical pericardial window creation with relief of tamponade symptoms. In one other reported case of pericardial tamponade in a patient who had undergone pneumonectomy, the sub-xiphoid approach to pericardiocentesis was abandoned due to risk of hepatic injury, and instead utilized an apex approach under echocardiographic guidance.15

Increased awareness of potential cardiovascular toxicities of immune checkpoint inhibitor therapy may lead to quicker recognition and initiation of appropriate management including pericardial drainage, cessation of the offending agent and consideration of corticosteroid use.

CONCLUSION

Pembrolizumab therapy is associated with cardiovascular toxicity including pericardial effusion and cardiac tamponade. It is important to consider cardiac effusions as a cause of chest pain or dyspnea in patients with a history of malignancy, radiation, or immunotherapy. Additionally, patients with a history of pneumonectomy are at risk of intrathoracic rearrangements of normal anatomy. This can make diagnosis and treatment of cardiac tamponade difficult as usual approaches to pericardiocentesis may be difficult to obtain.
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Hyperglycemia and Hypoglycemia-Related Chorea in an 83-Year-Old Man

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ABSTRACT

We report a case of a patient who first presented with hyperglycemic chorea, and subsequently with hypoglycemic chorea. The patient's hypoglycemia was thought to be iatrogenic, highlighting the importance of careful glucose management following glycemia-related chorea. Presumably secondary to the patient's chorea, the patient also suffered from new onset shoulder pain, which was managed with gabapentin. Unfortunately, due to the patient’s renal failure, the gabapentin, combined with infection, led to encephalopathy in this patient. This report presents and offers useful tips on the management of a unique patient who suffered from hyperglycemic chorea, hypoglycemic chorea, and encephalopathy, all within a few weeks.

KEYWORDS: chorea, movement disorder, hyperglycemia, hypoglycemia

BACKGROUND

Chorea develops from disruptions in the cortico-striato-pallido-thalamic circuit, leading to disinhibition of movement. Chorea is classically said to result from lesions to the subthalamic nucleus (STN), though it is in fact more commonly secondary to striatal, thalamic, or motor cortex lesions due largely to the higher incidence of strokes in these regions. Further, striatal changes on imaging are nearly universally found in cases of glycemic control related chorea.1,3

Chorea is a relatively uncommon syndrome, seen in approximately 1% of patients at some motor disorders clinics.4 The differential diagnosis for chorea includes over 20 hereditary causes5 and many acquired ones. While considerable overlap exists, hereditary causes tend to occur in younger patients (<60 years old) and can have accompanying syndromic symptoms. Huntington’s disease is the overall most common cause of hereditary chorea, with an estimated prevalence of 1 in 10,000 people,5 though other hereditary causes may reach similar prevalence within specific ethnic groups, such as dentatorubral pallidoluysian atrophy in Japanese patients.6

Acquired causes of chorea can be grouped into cerebrovascular, autoimmune/inflammatory, endocrine, neoplastic, metabolic, infectious, drug-induced, toxic, or other causes, with several etiologies falling under each of these. Among acquired causes of chorea, vascular injury, hyperglycemia or hypoglycemia, drug-induced chorea (particularly secondary to neuroleptics), Sydenham’s chorea (secondary to group A beta-hemolytic strep infection), and AIDS-associated chorea (particularly HIV encephalitis and toxoplasma infection) are among the most frequently seen, though the relative frequency of these causes varies widely across case series.1,4,7

Initial workup of new onset chorea in an older patient with a negative family history and taking no neuroleptic medications should therefore focus on ruling in or out the likely and urgent etiologies of vascular injury and hyper- or hypoglycemia through labs and neuroimaging. Further workup of irreversible, lower likelihood, and/or less urgent causes (e.g. Lyme antibody testing, ceruloplasmin levels, autoimmune panels, etc.) should be reserved for patients whose history and physical exam raise suspicion for these specific etiologies or whose etiology remains unclear after initial workup.

CASE REPORT

An 83-year-old patient presented with large amplitude, left-sided, choreiform movements of the face, arm, and leg. The patient reported that these symptoms began one week prior and worsened while he was receiving hemodialysis for end-stage renal disease (ESRD). He denied any temporal pattern, exacerbators, or alleviators of his symptoms. Additionally, he denied any headache, vision changes, confusion, speech difficulty, nausea, seizures, falls, or new balance or gait disturbances and denied ever smoking or frequent alcohol consumption.

The patient had a past medical history which included: current ESRD treated with hemodialysis, heart failure with reduced ejection fraction [25%, measured eight months prior] status-post NSTEMI, type II diabetes, a one-year prior history of surgically treated colonic malignancy, and a remote history of renal cell carcinoma with nephrectomy. The patient’s current medications included: atorvastatin, glimepiride, metformin, acetaminophen, aspirin, and sublingual nitroglycerin.

The patient’s vitals and labs are summarized in Table 1. On physical exam, he appeared comfortable despite his involuntarily left-sided movements. His cranial nerve exam
was normal except for difficulty with puffing out his cheeks. Finger to nose was intact, 2+ patellar reflexes, no ankle clonus, and Babinski was down-going. He was able to recall one word on three-word recall and showed unsteady gait. His Romberg was intact with no pronator drift. No abnormalities were noted on HEENT, cardiovascular, respiratory, abdominal, or extremity exams.

CT revealed increased attenuation in the right putamen and globus pallidus (Figure 1) as well as small vessel ischemic changes and evidence of a previous left parietal occipital infarction. Subsequent MRI similarly revealed T1 hyperintensity in the right corpus striatum, though image quality was limited by movement. BMP was normal besides a chloride of 96, creatinine of 1.74, glucose of 208, and anion gap of 14. CBC was normal besides a hemoglobin of 10.8, likely secondary to the patients pre-existing renal dysfunction associated anemia. Given the patients plasma glucose of 208 and imaging findings, hyperglycemic chorea was deemed the most likely etiology.

The first priority in the management of patients with hyperglycemic chorea is glucose and electrolyte control. Until recovery, and in patient’s whose symptoms persist, similar agents to those used in Huntington’s chorea, including neuroleptics such as olanzapine, risperidone, tiapride, or haloperidol and dopamine depleting agents such as tetrabenazine, deutetrabenazine, or valbenazine, are typically used.3,8

In our patient, blood glucose was monitored and controlled, and the patient was treated with olanzapine and a short course of clonazepam. Given the patient’s renal failure, metformin was discontinued for the management of his diabetes. Despite potential interactions with the patient’s renal failure, glimepiride was continued. At discharge the next day, the patient’s face or leg movements were no longer present though occasional large amplitude arm movements persisted.

Approximately two months after discharge, our patient returned to the hospital with a blood glucose of 44, measured at home, and recurrence of his left-sided chorea, accompanied by left-sided shoulder and arm pain (suspected secondary to choreiform movements), and failure to thrive at home. Physical exam revealed tenderness over the left anterior rotator cuff and shoulder MRI showed evidence of inflammation, though image quality was limited by patient movement. 100mg of gabapentin, three times per day, was prescribed to help with the shoulder pain. The hypoglycemia was suspected to be secondary to glimepiride use which was subsequently held, discontinued, and replaced with insulin on a sliding scale with a goal glucose of 120–180. Glucose stabilization led to symptom improvement, albeit without complete remission, and the patient was discharged to a skilled nursing facility. Unfortunately, two weeks later, the patient returned with a clostridioides difficile infection, pneumonia, and urinary tract infection, and accompanying encephalopathy, suspected to be multifactorially secondary to the patient’s gabapentin and infections. The patient was treated with antibiotics and his gabapentin dose was decreased to 100mg three times per week and he rapidly recovered.

**DISCUSSION**

While approximately 85% of patients will recover from hyperglycemic chorea within the first month,3 outcomes vary widely. One review, for example, reported patients ranging in their length of symptom duration from <2 days to

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**Table 1. Vitals and lab values for the patient at initial presentation for hyperglycemic chorea and at second presentation for hypoglycemic chorea.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit 1</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>36.7°C</td>
<td>37.5°C</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>119/58mmHg</td>
<td>111/52 mmHg</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>O2 Saturation</td>
<td>100% on room air</td>
<td>97% on room air</td>
</tr>
<tr>
<td>Glucose</td>
<td>208mg/dl</td>
<td>111mg/dl (44mg/dl prior to arrival at hospital)</td>
</tr>
<tr>
<td>Sodium</td>
<td>136mEq/L</td>
<td>133mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.9mEq/L</td>
<td>3.8mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>96mEq/L</td>
<td>93mEq/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.74mg/dL</td>
<td>5.39mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.8g/dL</td>
<td>9.4g/dL</td>
</tr>
</tbody>
</table>

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**Figure 1.** Horizontal CT image showing increased attenuation in the right putamen and right globus pallidus (red arrow).
>5 years. While their results did not reach significance, in reviewing the literature, this same study found preliminary indications that extension of neuroimaging findings beyond the putamen as well as female sex predicted longer symptom persistence. When these same analyses included stroke patients with chorea in addition to hyperglycemic chorea cases, increasing the power of the analyses without substantially shifting the effect sizes, these same predictors offered significant prognostic value. While no prior reports have documented a single individual suffering from both hyper- and hypo-glycemic chorea, their review did note symptom recurrence to occur in 11/236 (5%) cases they reviewed as well as in 3/11 (27%) of their original cases.1

Interestingly, extreme variation in glucose is not necessarily required for symptoms to emerge. In Lee et al’s case series of 14 patients for example, two (14%) had euglycemia (blood glucose between 90mg/dl and 150mg/dl) at time of glucose measurement and five (36%) had glucose measured between 150mg/dl and 250mg/dl. Only 3/14 (21%) of their patients had glucose >400mg/dl.1 Our patient’s presentation with a blood glucose of 208 is therefore not atypical of patients with hyperglycemic chorea.

The precise mechanisms underlying glycemic control-related chorea remain unclear, though several theories have been proposed including hyperglycemia causing alterations in gamma-aminobutyric acid (GABA) metabolism, osmotic changes, ischemia, calcification, petechial hemorrhages, and gemistocytes formation (reactive swollen astrocytes).8 Interestingly, the theory that the brain may metabolize GABA under energy restricted conditions, disinhibiting the thalamus and causing chorea, may explain why an estimated 91% of hyperglycemic chorea cases specifically involve non-ketotic hyperglycemia [NKH],3 though it does not explain hypoglycemic or hyperglycemic hyperketotic chorea. These theories also leave many questions unanswered, such as why the vast majority of cases of glycemia-related chorea lead to unilateral symptoms or why only a very small subset of patients with hyperglycemia develop symptoms.

The present case presents a patient who suffered first from hyperglycemic chorea but whose glucose control subsequently led to iatrogenic hypoglycemia which provoked recurrence of his chorea symptoms, highlighting the importance of careful glucose management in patients who have suffered from hyperglycemic chorea. This case also highlights the potential for joint irrigation secondary to choreiform movement as well as the importance of adjusting gabapentin dosing in patients with renal failure.

References

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Safety and Feasibility of Ultra-Restrictive Transfusion Protocol as a Blood-Preservation Strategy During Shortage Crises

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ABSTRACT

BACKGROUND: We hypothesized that implementation of new ultra-restrictive transfusion protocol in adult surgical intensive care units (SICU) was safe and feasible during pandemic-associated shortage crises.

METHODS: Retrospective analysis two months pre- and post-implementation of ultra-restrictive transfusion protocol in March 2020 with hemoglobin cutoff of 6 g/dL (6.5 g/dL if ≥ 65 years old) for patients without COVID, active bleeding, or myocardial ischemia.

RESULTS: We identified 16/93 and 27/168 patients PRE and POST meeting standard transfusion threshold (7 g/dL); within POST, 12 patients met ultra-restrictive cutoffs. There was no significant difference between PRE and POST in the rate of mortality, ischemic complications, or the number of transfusions per patient, however, the overall incidence of transfusion was lower in the POST group (7.1 vs 17.2%, p = 0.02). Patients received a mean (SD) of 4(3.8) and 2.4(1.5) PRBC transfusions pre- and post-implementation. Odds ratio of mortality in POST group was 0.62 (95%CI: 0.08-5.12) adjusted for age, sex, and SOFA score.

CONCLUSIONS: Implementation of an ultra-restrictive transfusion protocol was feasible and effective as a blood-preservation strategy.

KEYWORDS: COVID-19; transfusion; crisis; pandemic; blood products

BACKGROUND

The COVID-19 pandemic presented innumerable, well-documented challenges to healthcare systems including the cancellation of elective surgeries,1 delayed diagnosis and treatment of patients with malignancy,2 disruptions in the management of time-sensitive emergencies including myocardial infarction and stroke,3 and disruptions in the delivery of routine and emergency psychiatric care.4 With a dramatic rise in hospital admissions secondary to COVID-19 pneumonia and acute respiratory distress syndrome, there was a significant reduction in supply of medical equipment and medications.5,7 During the first wave of COVID-19 in March 2020, the majority of public health attention and efforts were rightly focused on containment as well as the triage and treatment of patients with active infection. However, we anticipated that other patients with critical illness would also suffer secondary to the increased consumption of scarce resources, including blood products.

Hesitancy among the general population to donate blood early in the pandemic resulted in a significant and sharp decline in the number of donations and available blood products in hospitals across the nation.6,11 In March 2020, the American Red Cross reported receiving 86,000 fewer blood donations “due to an unprecedented number of blood drive cancellations” and media reports of critical shortages in cities including New York City alarmed intensivists around the world.12,13 In Rhode Island, a similar increase in mobile blood drive cancellations was attributed to individuals’ fear of being in public spaces amid the evolving pandemic.14 The Rhode Island Blood Center reported that the widespread cancellation of mobile drives resulted in a 50% decrease in the pre-pandemic supply of blood donors and that maintenance of an adequate blood supply would require 100% occupancy of expanded appointment times by individual donors at donation centers.15 This shortage threatened patients who could require emergency transfusion for traumatic or obstetric hemorrhage as well as those requiring routine blood transfusions for chronic hematologic and oncologic diseases.

Recognizing the importance of maintaining an adequate stockpile of blood products, we joined our colleagues across the country in exploring ways to preserve blood products.16,17 In addition to attempting to increase the available supply through hospital-based blood drives, we aimed to curtail the demand by reducing over-utilization of red cell transfusion in the inpatient setting among patients with anemia of critical illness. In March 2020, we implemented an ultra-restrictive protocol by reducing the hemoglobin threshold for transfusion in the surgical intensive care units (SICU) in the setting of a declared state of emergency. We thus aimed to examine the safety and feasibility of the protocol for patients as well as its efficacy in preserving blood products through a proof-of-concept study. We hypothesized that the adoption of an ultra-restrictive transfusion protocol in surgical intensive care units is safe and feasible compared with standard transfusion practices and is effective as a blood-preservation strategy during times of critical shortage.
METHODS

Effective March 20, 2020, our division implemented an ultra-restrictive transfusion protocol by decreasing the transfusion threshold in our SICUs compared to our standard practice threshold of 7 g/dL. We established a new threshold of 6 g/dL for patients younger than 65 years old and 6.5 g/dL for those 65 years old or older. Patients were transfused with 1 unit of PRBC when they met the cutoff. The ultra-restrictive protocol excluded patients who tested positive for SARS-CoV-2, had active bleeding, or who had signs of ongoing myocardial ischemia based on anginal symptoms or electrocardiographic changes. The protocol was adopted along with other measures of an overall blood-preservation strategy including the recommendation to limit routine daily blood draws in accordance with best practices in critical care. Though patients with active hemorrhage were excluded from this analysis of the impact of the ultra-restrictive threshold, an additional aspect of our overall strategy was to review the indications for massive transfusion protocol activation on a case-by-case basis. If activation of the massive transfusion protocol was deemed futile, then blood product resuscitation was planned to be withheld. Fortunately, however, this portion of the protocol remained purely hypothetical and there were no cases where massive transfusion was withheld due to the blood shortage. All physicians providing patient care in the SICU during the study period were notified of the immediate implementation of the ultra-restrictive protocol beginning on March 20th, 2020. The protocol remained continuously active for the duration of the study period.

After constructing the study concept, we obtained an Institutional Review Board approval prior to collecting the data (Lifespan IRB#1610422). The ultra-restrictive protocol was developed urgently in response to impending blood shortage crises facing our intensive care units, and clinical implementation of the protocol preceded the formulation of this associated research hypothesis. Thus, the informed consent requirement was waived for the retrospective review of prospectively collected clinical data. We then proceeded to perform a single-center, retrospective cohort study of all adult patients admitted to surgical intensive care units at Rhode Island Hospital two months before (PRE) and after (POST) implementation of the new protocol. Thus, our sample included critically ill patients admitted to either the general surgical or trauma intensive care unit who received both operative as well as nonoperative management. Though elective surgeries were paused during the majority of the post-implementation study period, there was no difference in surgical practice between groups with respect to intraoperative blood-preservation strategies nor the decision to proceed with urgent or emergency surgery among patients admitted to the intensive care unit.

Our primary outcome was in-hospital mortality. Secondary outcomes included the incidence of packed red blood cells (PRBC) transfusion in our SICUs, the number of transfusions per patient, and the development of ischemic complications, defined as the occurrence of clinically significant acute myocardial, cerebral, mesenteric, or limb ischemia. We used multiple logistic regression to adjust our mortality outcome for age, sex, and Sequential Organ Failure Assessment (SOFA) score to capture patients’ overall level of critical illness and organ dysfunction. We also performed a pre-specified analysis of patients who were transfused according to the standard protocol within the PRE group compared with those in the POST group who would have qualified for transfusion based on the standard threshold (7 g/dL) but did not meet the new ultra-restrictive criteria for transfusion. Categorical data were analyzed using Chi-square and reported as frequencies and percentages. Parametric continuous variables were analyzed using Student’s t-test. Nonparametric continuous data were analyzed using Wilcoxon-Rank Sum test. These are presented as medians or averages with interquartile range (IQR) or percent as appropriate. All statistical analyses were conducted with a significance level of 0.05.

RESULTS

Our study cohort included 261 patients, of whom 93 were admitted to an SICU before implementation of the protocol (PRE) and 168 were admitted thereafter (POST). Within the PRE group, 16 patients (17.2%) experienced a hemoglobin drop below 7 g/dL and received red cell transfusion per standard protocol. Within the POST group, 27 patients (16.1%) had a hemoglobin drop beneath the standard transfusion threshold. Of these, 12 patients (44.4%) met the ultra-restrictive cutoffs and subsequently received transfusion according to the new protocol. Overall, the percentage of SICU patients who received PRBC transfusion was significantly lower in the POST group (7.1% versus 17.2%, p = 0.02), (Figure 1).

Among those who met the transfusion cutoff, we observed no statistically significant differences between the two groups with respect to age, sex, medical comorbidities, and SOFA score (Table 1). Similarly, there was no significant difference in the ICU length of stay or time-to-transfusion between those pre- and post-implementation of the ultra-restrictive protocol. For the primary outcome, there was no statistically significant difference in the rate of in-hospital mortality between transfused patients within the PRE and POST groups (31.3% vs 25.0%, p = 1). Likewise, we observed no significant difference in the rate of ischemic complications (12.5% vs 33.3%, p = 0.35) or the number of PRBC units transfused per patient (4.0 vs 2.4, p = 0.21) between transfused patients within the PRE and POST groups, respectively. On multiple logistic regression adjusting for age, sex, and SOFA score, the odds ratio for in-hospital mortality within the POST group was 0.62 (95% CI: 0.08 to 5.12).
Within the POST group, there were 15 patients who were eligible for transfusion based on the standard threshold after experiencing a hemoglobin drop below 7 g/dL but failed to ultimately meet the ultra-restrictive cutoffs implemented during the shortage crisis. Compared with patients transfused according to the standard protocol in the PRE group, these patients were significantly younger (49 vs 63 years old, \( p = 0.02 \)). However, we observed no statistically significant difference in the proportion of patients greater than 65 years old. Though there were no statistically significant differences in other baseline characteristics between these groups (Table 2), the “standard-eligible” yet non-transfused patients within the POST group were observed to have a lower rate of trauma and a higher rate of chronic anemia. For outcomes, we observed no significant differences in the rates of in-hospital mortality (13.3 vs 31.3%, \( p = 0.39 \)) or ischemic complications (20.0 vs 12.5%, \( p = 0.65 \)) between the non-transfused patients with hemoglobin drop below 7 g/dL in the POST group and patients transfused for hemoglobin drop below 7 g/dL within the PRE group, respectively. On multiple regression controlling for age, sex, and SOFA score, the adjusted odds for in-hospital mortality among these standard-eligible, non-transfused patients compared to the PRE group was 0.37 (95% CI: 0.05 to 2.95).

### Table 1. Comparison of characteristics and outcomes of patients who met transfusion cutoffs Pre- and Post-implementation of ultra-restrictive protocol.

<table>
<thead>
<tr>
<th></th>
<th>PRE (n=16)</th>
<th>POST (n=12)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>64 (14)</td>
<td>69 (18)</td>
<td>0.41</td>
</tr>
<tr>
<td>Age ≥ 65 years, n (%)</td>
<td>7 (43.8)</td>
<td>9 (75.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>8 (50.0)</td>
<td>8 (66.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Trauma admission, n (%)</td>
<td>9 (56.3)</td>
<td>9 (75.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Past Medical History, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>2 (13.3)</td>
<td>1 (8.3)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (18.8)</td>
<td>4 (33.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (68.8)</td>
<td>8 (66.7)</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (12.5)</td>
<td>1 (8.3)</td>
<td>1</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2 (12.5)</td>
<td>3 (25.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (12.5)</td>
<td>0 (0)</td>
<td>0.49</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.18</td>
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<tr>
<td>Chronic anemia</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>SOFA score, median [IQR]</td>
<td>3 [1, 4]</td>
<td>5 [2, 8]</td>
<td>0.26</td>
</tr>
<tr>
<td>ICU LOS (days), median [IQR]</td>
<td>7 [5, 18]</td>
<td>6 [5, 13]</td>
<td>0.67</td>
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<tr>
<td>Hospital LOS (days), median [IQR]</td>
<td>13 [8, 26]</td>
<td>13 [10, 20]</td>
<td>1</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>5 (31.3)</td>
<td>3 (25.0)</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic complications, n (%)</td>
<td>2 (12.5)</td>
<td>4 (33.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>PRBC transfusions per patient (units), mean (SD)</td>
<td>4.0 (3.8)</td>
<td>2.4 (1.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Time-to-transfusion (days), median [IQR]</td>
<td>2 [1, 4.5]</td>
<td>2.5 [2, 6]</td>
<td>0.27</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of characteristics and outcomes of between patients with hemoglobin drop below 7 g/dL Pre-protocol and those in Post-protocol group with hemoglobin below 7 but did not meet the new ultra-restrictive transfusion cutoff.

<table>
<thead>
<tr>
<th></th>
<th>PRE (n=16)</th>
<th>POST (n=15)</th>
<th>( P ) value</th>
</tr>
</thead>
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<tr>
<td>Age (years), mean (SD)</td>
<td>63 (14)</td>
<td>49 (17)</td>
<td>0.02</td>
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<tr>
<td>Age ≥ 65 years, n (%)</td>
<td>7 (43.8)</td>
<td>3 (20.0)</td>
<td>0.30</td>
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<tr>
<td>Sex (male), n (%)</td>
<td>8 (50.0)</td>
<td>12 (80.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Trauma admission, n (%)</td>
<td>9 (56.3)</td>
<td>4 (26.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Past Medical History, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (18.8)</td>
<td>1 (6.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (68.8)</td>
<td>6 (40)</td>
<td>0.16</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (12.5)</td>
<td>2 (13.3)</td>
<td>1</td>
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<td>Atrial Fibrillation</td>
<td>2 (12.5)</td>
<td>0 (0)</td>
<td>0.48</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (12.5)</td>
<td>2 (13.3)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Chronic anemia</td>
<td>0 (0)</td>
<td>3 (20.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>SOFA score, median [IQR]</td>
<td>3 [1, 4]</td>
<td>5 [2, 6]</td>
<td>0.25</td>
</tr>
<tr>
<td>ICU LOS (days), median [IQR]</td>
<td>6 [5, 18]</td>
<td>7 [5, 14]</td>
<td>1</td>
</tr>
<tr>
<td>Hospital LOS (days), median [IQR]</td>
<td>13 [8, 26]</td>
<td>16 [7, 31]</td>
<td>0.58</td>
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<tr>
<td>In-hospital mortality, n (%)</td>
<td>5 (31.3)</td>
<td>2 (13.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Ischemic complications, n (%)</td>
<td>2 (12.5)</td>
<td>3 (20.0)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

ABB: ICU: Intensive care unit. LOS: Length of stay. SOFA: Sequential Organ Failure Assessment. PRBC: Packed red blood cells.
As noted, we did not observe a statistically significant difference in the mean (SD) number of PRBC units transfused per patient between the PRE and POST groups (4.0 [3.8] vs 2.4 [1.5], p = 0.21). Importantly, however, implementation of the ultra-restrictive protocol resulted in 15 of 27 eligible patients with hemoglobin drop below 7 g/dL not receiving any red cell transfusions. Considering the number of units transfused per patient prior to the implementation of the ultra-restrictive protocol, we estimated that 60 to 100 units of PRBCs were preserved during the two months of the protocol, reflecting a 55 to 73% reduction in PRBC utilization in our SICUs.

**DISCUSSION**

In our small, pragmatic, proof-of-concept study of the safety, feasibility, and efficacy of an ultra-restrictive transfusion protocol as a blood-preservation strategy during a pandemic-associated shortage crisis, we found that implementation of a new hemoglobin threshold of 6 g/dL (6.5 g/dL if ≥ 65 years old) for transfusion was feasible and effective in reducing the number of patients undergoing transfusion and overall PRBC utilization when compared with standard practice. Though we failed to observe significant differences in the rates of in-hospital mortality or ischemic complications, our small sample size and low statistical power limit our ability to meaningfully assess the safety of these ultra-restrictive thresholds outside of blood shortage crises.

The potential for critical blood shortage during crises – both natural and man-made – has been previously recognized and observed. Disaster experts have attempts to simulate blood-shortage scenarios and model potential interventions to mitigate the imbalance between supply and demand. Importantly, however, most models were developed to simulate the effects of short-term disasters, such as a terrorist attack or a natural disaster. These models focused on preemptively boosting hospitals’ supply to meet the short-term demand of massive transfusion needs. Often, during such crises, there is actually increased motivation among the public to donate blood. During the COVID-19 pandemic, however, the imbalance also resulted from a sustained and significant decrease in blood supply due to public fear of COVID-19 transmission surrounding blood donation.

At our center, we observed that the demand for blood products remained relatively stable to slightly increased. Considering the limited shelf life of PRBCs, contingency plans to boost supply are not sustainable solutions during extended periods of blood shortage, establishing the need for long-term interventions. Investigators in Melbourne, Australia have reported a simulation model for prolonged disasters. Though their model was limited in duration to 21 days, they found that restricting PRBC transfusion resulted in a 28.5% reduction in utilization among patients with nonurgent indications. Our experience showed a higher potential reduction in PRBC utilization (55% to 73%) compared to our routine transfusion practices in the ICU, which comprise the majority of nonurgent transfusions in the inpatient setting. A validation of the actual reduction potential using mathematical modeling, applying our approach, should be performed to accurately predict the potential reduction in a large healthcare system.

Anemia among critically ill patients is common and multifactorial. Our results also provide preliminary evidence that suggests that ultra-restrictive transfusion protocols may be safe compared to standard practice in the ICU. Since the landmark TRICC trial in 1999, restrictive transfusion practices were found to be safe and effective compared to liberal practices. This was later confirmed to also be a safe strategy among specific ICU populations, including patients with septic shock and following cardiac surgery. Restrictive strategies were associated with decreased exposure to allogenic blood transfusions without an impact on mortality or morbidity. Considering the strong evidence, it became a standard practice to limit nonurgent blood transfusion in the ICU for patients by establishing a hemoglobin threshold of 7 g/dL, although the true threshold for critical anemia remains unknown. Evidence from patients with anemia who refuse blood transfusion demonstrate that an increased mortality rate is observed below a hemoglobin cutoff of 5 g/dL. However, evidence for establishing a hemoglobin threshold for transfusion below 7 g/dL among any patients remains sparse. One study reported using a hematocrit of 20% compared with 25% as an on-pump intraoperative transfusion threshold during coronary artery bypass grafting, thus limiting the generalizability of results to patients not undergoing cardiopulmonary bypass. Additionally, one study implemented a restrictive transfusion protocol with a hemoglobin threshold of 6.4 g/dL among low-risk orthopedic surgery patients under the age of 50 undergoing elective total hip or knee arthroplasty. However, their results were pooled across low- (< 50 years old), intermediate- (50 to 70 years old), and high-risk patients (70 years old) with separate transfusion thresholds of 6.4, 7.2, and 8.9 g/dL for each subgroup, respectively. Thus, in the absence of any evidence for transfusion thresholds below 7 g/dL among the critically ill, our ultra-restrictive threshold was determined by consensus agreement within our division. In order to establish a blood-preservation effect while remaining conservative and promoting patient safety, our protocol lowered the threshold to 6.0 g/dL for patients under the age of 65 and 6.5 g/dL for patients ≥ 65 years old. Though this small, single-center evaluation was under-powered to assess the difference in mortality and ischemic complications between groups, our results establish a need to further evaluate our current transfusion practices and consider whether similar ultra-restrictive thresholds may offer benefit, even outside of blood shortage crises. Of course, such validation would require multi-center, prospective evaluation of clinical outcomes.
as well as consideration of oxygen delivery and end-organ ischemia seen with lower hemoglobin levels.

Our study is not without significant limitations. First, this protocol was intended to remain active for a brief time during the COVID-19 pandemic during the highest period of resource demand at our institution. As a result, the number of patients who met the ultra-restrictive transfusion cutoff was small, resulting in low to very low statistical power to assess the primary and secondary outcomes. Though the ultra-restrictive protocol has been intermittently reactivated for use during additional periods of critical blood shortage following this study period, we chose to limit the timeframe for our analysis to increase the direct comparability of patient groups in the first days of the pandemic when the greatest strain was seen across the healthcare system.

Therefore, the findings that implementation of the new protocol was not associated with increased mortality or ischemic complications must be interpreted cautiously and only for the purpose of hypothesis generation. Additionally, we only included patients that were admitted to either the general surgical or trauma intensive care unit, which further limits the generalizability of our results to other critically ill populations. As a result, we cannot recommend widespread implementation of this protocol at institutions with predominantly non-surgical patients and different admitting diagnoses without further study and adequate validation. Importantly, though our multiple regression model was controlled for age, sex, and SOFA score, the presence of other confounding variables or effect modifiers including baseline hemoglobin cannot be excluded. Furthermore, we did not include an analysis of institution-wide utilization of blood products at our institution. Therefore, we cannot conclude definitively that the reduction in blood product utilization among our intensive care units directly resulted in the improved availability of blood products for other patients in the hospital. Despite these limitations, the results of our study highlight the potential of our transfusion protocol as a blood-preservation strategy during subsequent pandemic-associated shortages and other similar disasters where triage decisions must be made.

CONCLUSION

Our small, pragmatic, proof-of-concept study demonstrated that the implementation of an ultra-restrictive transfusion protocol as a blood-preservation strategy during a pandemic-associated shortage crisis was feasible and effective in reducing blood product utilization within the surgical intensive care units at our institution. Though we failed to observe a significant increase in the rate of adverse events, further validation is required to assess the safety of this strategy outside of other patient populations and outside of states of emergency. If our results are validated, an ultra-restrictive transfusion protocol may represent a viable strategy during future shortage crises.

References


Wild-type GIST: A Rare Cause of Gastrointestinal Bleed

VICTORIA NGUYEN, MD; GRIFFIN REED, MD; CHRISTOPHER WARD, MD; STEPHANIE CATANESE, MD

BACKGROUND
Gastrointestinal stromal tumors (GISTs) are rare mesenchymal neoplasms that represent 1-2% of primary gastrointestinal (GI) cancers.1-2 GISTs can occur anywhere along the GI tract; therefore, clinical presentation varies based on location of the tumor. Patients can present with GI bleeding, obstruction and/or abdominal pain; however, others are asymptomatic and the tumors are discovered incidentally.1,3 Surgical resection is the primary curative treatment.1,4 However, neoadjuvant and adjuvant tyrosine kinase inhibitors (TKIs) may be considered in those with a mutation in the KIT or platelet-derived growth factor alpha (PDGFRA) gene.5-9 For GISTs without a KIT or PDGFRA mutation, also referred to as wild-type GISTs, the benefits of TKIs are unclear.

CASE SUMMARY
The patient is a 74-year-old woman with a past medical history of irritable bowel syndrome, mitral valve prolapse, diabetes, hypertension, and hyperlipidemia who presented with melena, non-bloody, non-bilious emesis, and abdominal pain. Physical exam was notable for abdominal distension, dullness to percussion of the left half of the abdomen, and left upper quadrant tenderness. Admission labs were notable for a hemoglobin of 6.9 g/dL, white blood count of 5.2*10^9/L, and platelets of 254*10^9/L. Serum electrolytes and creatinine were within normal limits and BUN was elevated at 32 mg/dL. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed a large heterogenous mass in the left upper quadrant measuring 20.2 x 12.8 x 22.0 cm with a vascular pedicle arising from the greater curvature of the stomach. The spleen and left adrenal gland were also encased, with possible direct invasion.

The patient received a blood transfusion and was started on a proton pump inhibitor given presumed upper GI tract bleeding. Carcinoembryonic antigen and cancer antigen 19-9 tumor markers were negative. Upper endoscopy revealed vascular congestion in the gastric body but no evidence of mass or bleeding. Interventional radiology guided biopsy was positive for DOG-1 and CD117 (KIT) expression, which confirmed the diagnosis of GIST. Mitotic figures numbered up to 3 per 50 HPFs. Next-generation sequencing was negative for mutations in twenty-one genes, including KIT and PDGFRA. Additional chest imaging did not show metastatic disease.

DISCUSSION
Imaging of GISTs can reveal a heterogenous mass, often with different degrees of necrosis and cystic changes with possible enteric fistulation and calcification.10 These rare tumors often reach large sizes before symptoms like GI bleeding appear, seen in about 30% of cases.3 Confirmatory diagnosis is made from biopsy with immunohistochemical expression of KIT or DOG-1.1,11-12 Roughly 60% of patients are cured by surgery.13 However,
Figures 2A, B. Biopsy sample of GIST tumor, epithelioid variant. The rounded nuclei with abundant cytoplasm is epithelioid morphology. Pleomorphism is more common in epithelioid GIST compared to other types.

Figures 3A, B. Confirmatory IHC expression of CD117 (KIT) and DOG-1. In Figure 3A, a large vessel in the lower left is included for contrast, as it does not express CD117.

in this case, due to the tumor’s size and invasion into neighboring organs, upfront resection was not feasible. For patients with high tumor burden or high risk of recurrence, TKIs can be used to selectively inhibit receptor tyrosine kinases like KIT and PDGFRA. Interestingly, although 95% of GISTs over-express KIT, only 80% of GISTs contain KIT gene mutations. The second most common oncogenic drivers are PDGFRA mutations, seen in about 5–10% of tumors. Wild-type GISTs make up 10–15% of GISTs. Given the lack of mutation in the targeted receptor gene in wild-type GISTs, treatment of these tumors with TKIs is controversial. Some research suggests that alternative genes may be targeted. Additionally, although surgery is the only curative treatment, wild-type GISTs have a greater propensity to progress or recur despite complete surgical resection. Additional research is needed to further elucidate treatment options for wild-type GISTs and their unique molecular features.

References


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ABSTRACT
Throughout the COVID-19 pandemic, there has been growing but limited data describing the poor mortality outcomes in COVID-19 patients who experienced In-Hospital Cardiac Arrest (IHCA). This study evaluated the baseline characteristics and outcomes of COVID-19 patients who underwent cardiopulmonary resuscitation (CPR) during hospitalization in the early phases of the pandemic and compared them to that of several national and international centers. A list of all the IHCA events in the Lifespan hospital network from March 2020 to April 2021 was generated, and data, including de-identified patient characteristics, comorbidities, and details of the IHCA event, were examined. The primary outcome of all-cause mortality was then calculated. Forty-three patients with COVID-19 who experienced an IHCA event and underwent CPR were identified. Return of spontaneous circulation (ROSC) was achieved in 23 (53%) patients, and all-cause in-hospital mortality was 97.67%, with only one patient surviving until discharge. During the early pandemic, experiencing an IHCA event while admitted with COVID-19 carried an extremely poor prognosis, even if ROSC was achieved. This outcome likely reflects the lack of clear management guidelines or established therapeutic agents and the prevalence of the Delta strain during this time period.

KEYWORDS: COVID-19; CPR; In-Hospital Cardiac Arrest; ROSC; Mortality

BACKGROUND
Before the COVID-19 pandemic, the average IHCA survival-to-discharge rate in the United States was approximately 25%, predominantly in patients who experienced shockable rhythms (ventricular fibrillation and pulseless ventricular tachycardia).1,2 As the pandemic unfolded, investigators analyzing CPR outcomes in patients admitted with the original COVID-19 and Delta variant strains described survival-to-discharge rates much lower than the pre-pandemic average. Several single and multicenter studies reported that 3.6 - 66% of COVID-19 patients achieved ROSC, but IHCA and 30-day mortality remained persistently elevated.3,4,5,6 Interestingly, a US-based multicenter cohort found that 57.1% of COVID-19 patients achieved ROSC, and only 12.0% survived until discharge.7 This is in sharp contrast to the pre-pandemic rates. This study evaluated the baseline characteristics, and IHCA outcomes of all COVID-19 patients admitted to the Lifespan hospital network, a large tertiary referral system serving the tri-state confluence of southern New England (Rhode Island, Massachusetts, and Connecticut), to determine if they possessed a similar increased mortality risk as described in other regions.

METHODS AND DATA COLLECTION
This study is a retrospective analysis of pertinent baseline characteristics and mortality outcomes of COVID-19 patients who experienced an IHCA event while admitted with COVID-19 carried an extremely poor prognosis, even if ROSC was achieved. This outcome likely reflects the lack of clear management guidelines or established therapeutic agents and the prevalence of the Delta strain during this time period.

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Three investigators reviewed the electronic medical records (EMRs) of patients who experienced an IHCA event and identified those who also had a diagnosis of active COVID-19 infection. Active COVID-19 infection was defined as a known positive polymerase chain reaction (PCR) test anytime during the hospital admission in which the IHCA event occurred but prior to the event itself. Patients with COVID-19 infection prior to admission but with subsequent negative PCR tests upon the admission in which the IHCA event occurred were excluded from this study. Upon filtering IHCA events based on study exclusion criteria, the EMRs of included patients were reviewed, and de-identified patient data was collected into the study database. Collected data included patient baseline characteristics, e.g., age, sex, ethnicity, history of smoking, and comorbid conditions present upon admission. Comorbid conditions were defined as the documented diagnoses of the following diseases on
admission: cardiac (hypertension, coronary artery disease, chronic arrhythmias, congestive heart failure), pulmonary (chronic obstructive pulmonary disease, asthma, interstitial lung disease, pulmonary hypertension), endocrine (diabetes mellitus), or renal (chronic kidney disease, end-stage renal disease).

Additionally, data was collected on hospitalization complications present prior to IHCA and included the requirement of vasopressor support, invasive mechanical ventilation, or renal replacement therapy. Further, quantitative analysis to determine trends was performed of the cardiac rhythm at the time of IHCA, length of CPR (defined as the time from initiation of “Code Blue” until ROSC was achieved), CPR survival, post-IHCA vasopressor requirement, the total length of hospital stay, discharge disposition, 30-day mortality, and in-hospital mortality.

RESULTS

This study identified 43 patients with COVID-19 who experienced an IHCA event and underwent CPR within the defined time period. General patient characteristics are described in Table 1. The mean age was 66 years, with a range of 29–93 years. Among comorbid conditions, cardiac disease was the most common, with 33 patients possessing at least one cardiac diagnosis, followed by 15 patients with diabetes and 12 patients with a pulmonary condition. Of the 43 patients, 4 patients had known thromboembolic disease, and 3 patients were on renal replacement therapy.

At the time of IHCA, 90.6% of patients did not require vasopressor support, and 41.8% of patients required invasive mechanical ventilation. The predominant cardiac rhythms at the time of IHCA were pulseless electrical activity (PEA), identified in 32 (74.4%) patients, and asystole in 4 (9.3%) patients. The remaining cardiac rhythms are outlined in Table 2.

Table 1. Characteristics of COVID-19 patients who underwent CPR.

| General Characteristics | | |
|-------------------------|-------------------|
| **Age**                | **Years** |
| Mean Age               | 66 |
| Range Age              | 29–93 |
| Median Age             | 66 |
| **Gender**             | **Number of Patients** | **Percent of Total** |
| Female                 | 16 | 37.20% |
| Male                   | 27 | 62.70% |
| **Ethnicity**          | **Number of Patients** | **Percent of Total** |
| Hispanic/Latino        | 17 | 39.50% |
| Non-Hispanic/Latino    | 26 | 60.40% |
| **History of Smoking** | **Number of Patients** | **Percent of Total** |
| Yes                    | 25 | 58.10% |
| No                     | 17 | 39.53% |
| Unknown                | 1 | 2.33% |

Table 2. Characteristics of IHCA Events of COVID-19 Patients.

<table>
<thead>
<tr>
<th>Cardiac Arrest Characteristics</th>
<th>Number of Patients</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>32</td>
<td>74.42%</td>
</tr>
<tr>
<td>Asystole</td>
<td>4</td>
<td>9.30%</td>
</tr>
<tr>
<td>V-Fib</td>
<td>2</td>
<td>4.65%</td>
</tr>
<tr>
<td>Pulseless V tach</td>
<td>3</td>
<td>6.98%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>4.65%</td>
</tr>
<tr>
<td><strong>Code Duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Duration</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>Range Duration</td>
<td>2–90</td>
<td></td>
</tr>
<tr>
<td><strong>Vasopressor Requirement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to Arrest</td>
<td>39</td>
<td>90.70%</td>
</tr>
<tr>
<td>After Arrest</td>
<td>27</td>
<td>63.79%</td>
</tr>
<tr>
<td><strong>Mechanical Ventilation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to Arrest</td>
<td>26</td>
<td>60.47%</td>
</tr>
<tr>
<td><strong>Number of Arrests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Arrests</td>
<td>1.65</td>
<td></td>
</tr>
<tr>
<td>Range Arrests</td>
<td>1–8</td>
<td></td>
</tr>
<tr>
<td>Median Arrests</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Outcomes of IHCA Events of COVID-19 Events.

<table>
<thead>
<tr>
<th>Cardiac Arrest Outcomes</th>
<th>Days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay (LOS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LOS</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Range LOS</td>
<td>1–43</td>
<td></td>
</tr>
<tr>
<td>Median LOS</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td><strong>ROSC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patients</td>
<td>23</td>
<td>53%</td>
</tr>
<tr>
<td>Achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-Day Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>2.33%</td>
</tr>
<tr>
<td>No</td>
<td>42</td>
<td>97.67%</td>
</tr>
<tr>
<td>In-Hospital Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42</td>
<td>97.67%</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>2.33%</td>
</tr>
</tbody>
</table>
DISCUSSION

These results indicate that, within the Lifespan hospital network, a patient hospitalized with COVID-19 between March 2020 to April 2021 who experienced an IHCA event had just above a 50% probability of surviving CPR, and overall, a very poor prognosis, as only one patient survived until hospital discharge. The findings of this study reflect similar trends to the previously published COVID-19 IHCA mortality outcomes during that time period. For example, in April 2020, Shao et al published one of the first studies describing IHCA outcomes of COVID-19 patients over the period of January to February 2020 in Wuhan, China. Their study reported ROSC was achieved in 13.2% of patients, and only 2.9% of patients survived for 30 days.7 In late 2020, Thapa et al described a 53.7% rate of ROSC among COVID-19 patients who experienced an IHCA event and a 100% in-hospital mortality rate.8 In the United States, Mitchell et al conducted a multicenter retrospective cohort study of COVID-19 patient IHCA outcomes covering March through May 2020 and described a rate of ROSC in only 22.3% of patients, with a 12.3% 30-day survival rate.4

The authors suspect COVID-19 infection to be a catalyst for IHCA and the worsened mortality outcomes. This was supported by the lack of vasopressor requirement in the majority of patients at the time of IHCA, nearly half of all patients requiring mechanical ventilation at the time of arrest, and that PEA arrest was the most frequently observed rhythm upon cardiac arrest. These trends seem to suggest that IHCA in COVID-19 patients was likely driven by hypoxia from a respiratory infection and was likely compounded by the predominance of the highly virulent Delta strain as well as the lack of vaccination in the majority of patients during this time period. The first COVID-19 vaccines were not available until December 2020, and even then were relegated to high-risk patient populations.9,10 In addition, the healthcare workforce was primarily unvaccinated during most of the studied time period, and some questioned the safety of caregivers providing CPR to COVID-19 patients given the risk of viral transmission in the context of almost universally poor outcomes at the time. In some instances, this led to the ethnically supported universal “do not resuscitate” orders for COVID-19 patients.11 At the time, it would have been very appropriate to consider all this information while caring for COVID-19 patients and making decisions about the aggressiveness of end-of-life care.

LIMITATIONS

The implications and applications of this study are limited by several factors. First, this study reviews the beginning of the COVID-19 pandemic through April 2021, during which time the Delta strain was the most prevalent variant of the COVID-19 virus. Additionally, during that time period, there was an absence of clear guidelines on the management of COVID-19 infection, with only the last two months of this study overlapping with the formal recommendation of corticosteroids for COVID-19-induced hypoxia. As the pandemic progressed, additional COVID-19 treatments, including monoclonal antibodies, antiviral agents, and anticoagulation guidelines would be developed. These therapies greatly increased the clinical tools available for the treatment of COVID-19 infection, thereby lowering morbidity and mortality.12,13 Furthermore, the COVID-19 virus itself would continue to evolve, with the Omicron variant overtaking Delta as the dominant viral strain.14 For all these reasons, CPR outcomes observed in this study cannot be extrapolated to our current COVID-19 population.

Another limitation of this study is the absence of a comparison group for CPR survival in non-COVID-19 patients. In addition, only 11.63% of patients in this study experienced a shockable rhythm, nearly half of the pre-pandemic prevalence of IHCA shockable rhythms. As shockable rhythms are associated with improved outcomes, the comparison of this study’s results to that of the pre-pandemic survival rates is limited by the underrepresentation of these IHCA rhythms. This study is further limited by the small sample size. From the available population, the authors were only able to identify 43 patients with COVID-19 infection who experienced an IHCA event, which diminishes the generalizability of these results. Finally, this study is limited by the level of care which was reviewed. The IHCA data set reviewed by the authors is suspected to have omitted CPR performed on patients in the intensive care unit (ICU) and the emergency department (ED), as in both settings, an official “Code Blue” is not activated. Ippolito et al reported improved survival rates in a systematic review of COVID-19 IHCA events, observing an estimated mortality rate of 85.8% for IHCA occurring in the ICU, compared to a 95.5% mortality rate in non-ICU settings.15

CONCLUSION

During the early pandemic, patients hospitalized with COVID-19 infection who experienced an IHCA event carried an abysmal prognosis. The results of this study are consistent with prior national and international studies during the early Delta phase of the pandemic, suggesting an overall worsened multifactorial trend in COVID-19 patients. Larger studies are warranted to investigate factors contributing to these poorer outcomes and to compare these early IHCA mortality rates to a more recent time period which would include different variants, additional therapeutics, and a population with a higher vaccination rate. This information would be important for clinicians to consider as they discuss goals of care with patients admitted with COVID-19.
References


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Disclosures

The authors do not have any conflicts of interest.

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Brief Report: Health Equity and COVID-19 Prevention in the Manufacturing Industry

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**KEYWORDS:** COVID-19, manufacturing, workplace, disparities, guidelines

**INTRODUCTION**
The COVID-19 pandemic has caused substantial morbidity and mortality in the United States (US). Its economic impact has also been devastating, with most industries and age groups affected. Importantly, the economic impact of the COVID-19 pandemic has resulted in significant disparities including in case rates, hospitalizations, and deaths. These disparities also include economic impacts among Hispanic/Latino communities. These groups are more likely to work in lower-paying jobs including those in the manufacturing industry. Hispanic/Latino individuals may be more likely to work while sick due to the need for income and also potential pressure from employers. However, limited data exists on if individuals in work settings such as the manufacturing industry are working with COVID-19 symptoms, and the extent to which this occurs.

Efforts to mitigate COVID-19 transmission have included lockdowns, remote work, universal masking, physical distancing, testing and quarantine guidelines. Regular screening for COVID-19 symptoms and testing among employees is a critical component of prevention efforts, alongside isolation and quarantine policies for employees who test positive or experience close contact with a positive case. Nearly 84% of cases display some level of symptoms during their infection, and people with symptomatic infection are more likely to be infectious, reinforcing the importance of protocols and supports for avoiding in-person work while symptomatic. The manufacturing industry specifically has faced challenges, as some facilities have been unable to shut down or allow employees to work remotely due to the nature of their operations.

**DEVELOPMENT**
To explore whether individuals with symptoms present to work and the extent to which this happens, we conducted a cross-sectional study of COVID-19 cases reported to Rhode Island Department of Health (RIDOH) from March 1 to September 18, 2020. We also evaluated race and ethnicity to determine the extent to which disparities contributed to symptom presentation. We reviewed employer and workplace information, defining industry type according to the North American Industry Classification System. We defined whether workplace cases were associated with a major workplace outbreak or cluster. An outbreak was a workplace with at least five cases in a 14-day period with known epi-linked transmission from contact tracing and spread. A cluster was at least two cases within 14 days in one workplace. We identified whether manufacturing employee cases were likely to have worked while symptomatic based on self-reported dates of symptom onset, last day worked, and positive test specimen collection. If a case reported working within the 48-hours prior to symptom onset or positive test specimen collection date, we classified them as working while infectious based on estimates of incubation period which indicate that a person can unknowingly be infectious 48 hours prior to symptom onset.

We compared sociodemographic characteristics and symptom status/timing of non-manufacturing and manufacturing cases using Chi-Square tests. Among symptomatic manufacturing employee cases, we estimated the association between sociodemographic characteristics and symptom timing and working while infectious using bivariate and multivariable logistic regression. We analyzed data using SAS version 9.4 (Cary, North Carolina). Statistical inferences were based on significance p<0.05. This study was exempt from the Rhode Island Dept. of Health (RIDOH) Institutional Review Board.

From March 1 to September 14, 2020, there were 16,239 cases of COVID-19 that met inclusion criteria of which 1,499 (9.2%) were employees in manufacturing. Among symptomatic manufacturing employee cases, we estimated the association between sociodemographic characteristics and symptom timing and working while infectious using bivariate and multivariable logistic regression. We analyzed data using SAS version 9.4 (Cary, North Carolina). Statistical inferences were based on significance p<0.05. This study was exempt from the Rhode Island Dept. of Health (RIDOH) Institutional Review Board.

From March 1 to September 14, 2020, there were 16,239 cases of COVID-19 that met inclusion criteria of which 1,499 (9.2%) were employees in manufacturing. Among symptomatic manufacturing employee cases, 272 (20.1%) reported onset of COVID-19 symptoms prior to last day worked and were thus “working while symptomatic”. Symptomatic manufacturing cases were more likely to speak Spanish at home than those who did not work while symptomatic (51.8% vs 23.4%, p=0.0001). Those who did work while symptomatic were more often symptomatic prior to SARS-CoV-2 testing (77.9% vs. 70.7%) (Table 2).

Symptomatic manufacturing employees who primarily spoke Spanish had higher odds of having worked while symptomatic/infectious than those who primarily spoke English at home (adjusted odds ratio [aOR]=2.2, 95%
Table 1a. Sociodemographic and symptom characteristics of general and manufacturing employee COVID-19 cases in Rhode Island, March 1 to September 14, 2020. All race/ethnicity groups except for Hispanic/Latino, Declined, and Unknown reported non-Hispanic ethnicity or had unknown ethnicity information.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases Other Than Manufacturing (n=14740)</th>
<th>Manufacturing Cases (N=1499)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex Assigned at Birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8220</td>
<td>696</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>6496</td>
<td>801</td>
<td>0.44</td>
</tr>
<tr>
<td>Other/Declined</td>
<td>24</td>
<td>&lt;5</td>
<td>*</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–25</td>
<td>3232</td>
<td>178</td>
<td>0.0001</td>
</tr>
<tr>
<td>26–35</td>
<td>3588</td>
<td>357</td>
<td>0.38</td>
</tr>
<tr>
<td>36–45</td>
<td>3008</td>
<td>355</td>
<td>0.68</td>
</tr>
<tr>
<td>46–55</td>
<td>2959</td>
<td>391</td>
<td>0.04</td>
</tr>
<tr>
<td>56–64</td>
<td>1953</td>
<td>218</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino (any race)</td>
<td>6237</td>
<td>1049</td>
<td>0.0001</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>57</td>
<td>5</td>
<td>0.33</td>
</tr>
<tr>
<td>Asian</td>
<td>310</td>
<td>28</td>
<td>1.87</td>
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<td>Black or African American</td>
<td>1887</td>
<td>84</td>
<td>0.6</td>
</tr>
<tr>
<td>White</td>
<td>4279</td>
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<tr>
<td>Other race</td>
<td>144</td>
<td>11</td>
<td>0.73</td>
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<tr>
<td>Multiple races</td>
<td>110</td>
<td>5</td>
<td>0.33</td>
</tr>
<tr>
<td>Declined race</td>
<td>186</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Unknown/missing</td>
<td>1530</td>
<td>47</td>
<td>3.14</td>
</tr>
<tr>
<td><strong>Primary Language in Home</strong></td>
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<td></td>
</tr>
<tr>
<td>English</td>
<td>12053</td>
<td>1019</td>
<td>0.98</td>
</tr>
<tr>
<td>Haitian Creole</td>
<td>17</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Portuguese</td>
<td>85</td>
<td>19</td>
<td>1.27</td>
</tr>
<tr>
<td>Spanish</td>
<td>2089</td>
<td>428</td>
<td>28.55</td>
</tr>
<tr>
<td>Unknown/missing</td>
<td>467</td>
<td>18</td>
<td>1.2</td>
</tr>
<tr>
<td>Other</td>
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<td>0.6</td>
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<tr>
<td><strong>High Density Community (HDC) Resident</strong></td>
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<td></td>
</tr>
<tr>
<td>HDC Tier 1</td>
<td>7488</td>
<td>1014</td>
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</tr>
<tr>
<td>HDC Tier 2</td>
<td>2933</td>
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<td>16.55</td>
</tr>
<tr>
<td>Non-HDC</td>
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<td>186</td>
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</tr>
<tr>
<td>Unknown/missing</td>
<td>1049</td>
<td>45</td>
<td>3.02</td>
</tr>
</tbody>
</table>

*Excludes Congregate setting residents. Age group restricted to 16-64 years.

Table 1b. Symptom status in relation to COVID-19 testing for general and manufacturing employee COVID-19 cases in Rhode Island, March 1 to September 14, 2020.

<table>
<thead>
<tr>
<th>Symptom Status</th>
<th>Cases Other Than Manufacturing (n=14740)</th>
<th>Manufacturing Cases (N=1499)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Before Test</td>
<td>7899</td>
<td>975</td>
<td>0.04</td>
</tr>
<tr>
<td>At time of test</td>
<td>809</td>
<td>86</td>
<td>0.74</td>
</tr>
<tr>
<td>After Test</td>
<td>433</td>
<td>52</td>
<td>3.47</td>
</tr>
<tr>
<td>Out of Time Range*</td>
<td>572</td>
<td>62</td>
<td>4.14</td>
</tr>
<tr>
<td>Missing Onset Date or Specimen Collection Date**</td>
<td>1864</td>
<td>177</td>
<td>11.81</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Interviewed ***</td>
<td>931</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Unknown/missing</td>
<td>725</td>
<td>19</td>
<td>1.27</td>
</tr>
</tbody>
</table>

*Cases reporting symptoms starting more than 14 days before testing or more than 10 days after testing.
**A time frame cannot be established for cases who are missing either their date of symptom onset or their date of specimen collection.
***Out of state resident cases.

Confidence interval [CI]=1.3-3.8 (Table 3). Compared to those with symptom onset prior to positive test specimen collection, symptomatic manufacturing cases with symptom onset “out of range” had higher odds of working while symptomatic (aOR=3.4, 95%CI=1.5-7.9), while those with symptom onset at or after positive test specimen collection had lower odds of working while symptomatic (aOR=0.1, 95%CI=<0.1-0.2).

CONCLUSION
A significant number of COVID-19 cases in the manufacturing industry presenting to work were Spanish-speaking, highlighting disparities that exist in this setting. In general, cases were more likely to be male, older, Hispanic/Latino, primarily Spanish-speaking, and residents of dense and lower-income communities with high burdens of COVID-19. Approximately 20% worked while symptomatic. Nation-wide, Hispanic/Latinos have been more likely to acquire COVID-19 than Whites.1,2,3,7 Symptomatic people are likely to be more infectious, and may contribute to higher levels of ongoing transmission in the community.

Reasons why Hispanic/Latino individuals may work while symptomatic are diverse. Individuals may live paycheck-to-paycheck and face significant financial challenges if taken sick. Workers may also feel pressure to work by employers and be concerned about losing their job. Language...
Table 2. Sociodemographic and symptom characteristics among symptomatic manufacturing employee COVID-19 cases in Rhode Island who did and did not work while symptomatic, March 7 to September 14, 2020.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MFG cases did not work while symptomatic (N=1080)</th>
<th>MFG Cases worked while Symptomatic (N=272)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Sex Assigned at Birth</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>516</td>
<td>47.82</td>
<td>128</td>
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<tr>
<td>Male</td>
<td>563</td>
<td>52.18</td>
<td>144</td>
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<tr>
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<tr>
<td>16-25</td>
<td>131</td>
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<td>32</td>
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<tr>
<td>26-35</td>
<td>254</td>
<td>23.52</td>
<td>70</td>
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<tr>
<td>36-45</td>
<td>260</td>
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</tr>
<tr>
<td>46-55</td>
<td>290</td>
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<td>66</td>
</tr>
<tr>
<td>56-64</td>
<td>145</td>
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<td>41</td>
</tr>
<tr>
<td>Primary Language in Home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>801</td>
<td>74.37</td>
<td>127</td>
</tr>
<tr>
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<tr>
<td>Portuguese</td>
<td>12</td>
<td>1.11</td>
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<tr>
<td>Spanish</td>
<td>252</td>
<td>23.4</td>
<td>141</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
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<td>&lt;5</td>
</tr>
<tr>
<td>Symptom Timeline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Test</td>
<td>763</td>
<td>70.65</td>
<td>212</td>
</tr>
<tr>
<td>At Time of Test</td>
<td>83</td>
<td>7.69</td>
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</tr>
<tr>
<td>After Test</td>
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<td>4.81</td>
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</tr>
<tr>
<td>Out of Time Range*</td>
<td>41</td>
<td>3.8</td>
<td>21</td>
</tr>
<tr>
<td>Missing Onset Date or Specimen Collection Date**</td>
<td>141</td>
<td>13.06</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 3. Characteristics associated with working while symptomatic among symptomatic manufacturing employee COVID-19 cases in Rhode Island, March 7 to September 14, 2020. Significant values at p <0.05 are bolded.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bivariate Analysis*</th>
<th>Multivariate Analysis*</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Spanish</td>
<td>3.60</td>
<td>2.65</td>
</tr>
<tr>
<td>Other Language</td>
<td>1.26</td>
<td>0.42</td>
</tr>
<tr>
<td>Symptom Timeline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Onset: Before Test</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Symptom Onset: At or After Test</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptom Onset: Out of Time Range</td>
<td>1.73</td>
<td>0.99</td>
</tr>
<tr>
<td>Associated with Major Workplace Outbreak (Known Epi-Linked Transmission)</td>
<td>Yes</td>
<td>1.26</td>
</tr>
<tr>
<td>Associated with Workplace Cluster (2+ cases in 14 day period)</td>
<td>Yes</td>
<td>0.40</td>
</tr>
<tr>
<td>High Density Community (HDC) Resident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDC Tier 1</td>
<td>0.72</td>
<td>0.47</td>
</tr>
<tr>
<td>HDC Tier 2</td>
<td>0.62</td>
<td>0.36</td>
</tr>
<tr>
<td>Non-HDC</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.50</td>
<td>0.16</td>
</tr>
</tbody>
</table>

and cultural barriers may also result in reduced understanding of proper protocols and procedures. Nationally, the largest burden of COVID-19 cases falls on young Black or Hispanic/Latino males of lower economic status.4,7,9 These communities likely experience multiple factors that place them at higher risk for infection and worse outcomes, reinforcing the importance of culturally-competent messaging and accessible vaccination/testing.

Health disparities are costly societal burdens, and the pandemic provides a window of opportunity to build more equitable healthcare infrastructure.3,9 This holds true for manufacturing, which was recently demonstrated by this journal as having the highest incidence of workplace clusters of any industry within Rhode Island.10 Rhode Island has attempted to mitigate disparities seen with COVID-19 by providing free bilingual testing sites with more sites in certain neighborhoods.

In conclusion, symptomatic transmission of COVID-19 occurs in the manufacturing industry and is more prominent among underserved communities. This supports national data on racial and ethnic disparities for COVID-19 and highlights the need for improved public health efforts to support at-risk communities from COVID-19 including support in the workplace. Public health interventions should ensure employers of all industries may implement appropriate measures to prevent COVID-19 spread (e.g., masking and distancing) as the pandemic evolves.
References


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Aetna® is proud to support the Rhode Island Medical Journal.
Naloxone Recipients in Rhode Island, January 2019–March 2022
KRISTEN ST. JOHN, MPH; CHRISTINA HOM, MPH; HEIDI WEIDELE, MPH

BACKGROUND

In Rhode Island, 435 individuals lost their lives due to an accidental drug overdose in 2021, which is the highest ever recorded in state history.1 Overall, 375 of these deaths involved an opioid, including fentanyl.1 One strategy utilized by the Rhode Island Department of Health [RIDOH] to reduce opioid-involved fatalities is to distribute harm-reduction materials, such as naloxone, to individuals who use drugs.2

RIDOH monitors statewide naloxone distribution by capturing de-identified information on naloxone distribution conducted by community-based agencies, Rhode Island emergency departments, and pharmacies. Community-based agencies provide low- to no-barrier access to naloxone through community-based programs, including harm-reduction programs. Distributing naloxone to people who use drugs is a tool that can enhance client engagement and increase linkage to addiction treatment and other services. Hospital emergency departments are required to report information to our 48-Hour Reporting System on individuals receiving medical care for a suspected opioid overdose, which includes information on take-home naloxone kits dispensed upon discharge.

Pharmacies with a Controlled Substances Registration can also dispense naloxone. Pharmacies can dispense naloxone using standing orders, for which customers request naloxone directly from the pharmacy without a prescription, or by filling prescriptions written by providers. Rhode Island regulation requires that providers co-prescribe naloxone for patients with a history of opioid use disorder, those receiving an opioid (individually or in aggregate with other medications) greater than or equal to 50 morphine milligram equivalents per day, or those receiving an opioid and benzodiazepine prescription within 30 days of each other.3 Naloxone co-prescriptions are not required to be automatically renewed with each prescription renewal, as it is left to the providers’ clinical judgement, since they may be aware of a previous valid naloxone prescription or that a previously dispensed naloxone kit has not been used.

This study aims to describe recipients who received naloxone to better understand individuals who are accessing harm-reduction tools in the community.

METHODS

We analyzed records for naloxone distributed by hospitals, pharmacies, and community agencies from January 1, 2019 to March 31, 2022. As all data are de-identified, individuals who received multiple prescriptions or obtained naloxone from agencies multiple times may be counted more than once.

Prior to April 2021, naloxone distributed by community agencies was reported by agencies using Wufoo [a web application that allows users to create data-collection forms]. In April 2021, data collection was transferred to REDCap [REDCap, Vanderbilt]. Recipient type [business, NaloxBox, or individual] collection began in January 2022. To limit the analysis to individual encounters, records from businesses, training events, and NaloxBox units, which provide access to naloxone in buildings, as well as recipients of 24 or more naloxone doses (likely distributed for further distribution rather than individual use), were excluded. Of the 29,362 community distribution encounters that occurred during the study timeframe, 28,897 encounters remained in the final sample.

Rhode Island’s Prescription Drug Monitoring Program (PDMP) dataset contains information on pharmacy-dispensed naloxone. Records were obtained for 37,118 naloxone prescriptions dispensed during the study period.

Hospital staff are required to report individuals receiving emergency department care for a suspected opioid overdose within 48 hours of the visit via an online reporting system, which gathers information on take-home naloxone kits given to individuals. Records were obtained for 2,058 individuals who received naloxone kits distributed by hospitals.

In all datasets, frequencies were calculated for demographic variables, including gender, age group, and recipient’s municipality of residence. Municipalities of residence with less than 4% of the distribution for any source were aggregated into an ‘All Other Rhode Island Municipalities’ category. The community agency naloxone distribution and hospital datasets contain recipient race and ethnicity information, along with additional gender categories not collected by the PDMP. Since naloxone distributed by participating community agencies and hospitals is free to recipients, insurance type was only available for the PDMP. All datasets include out-of-state residents, who account for approximately 4.0% of the community, pharmacy datasets, and 9.9% of the hospital dataset. SAS Version 9.4 software was used for analyses [SAS Institute, Cary, NC].
RESULTS
From January 1, 2019 to March 31, 2022, hospital and pharmacy-based distribution to individuals remained relatively stable, while community-based agencies increased distribution by approximately 260% (Figure 1). For the entire timeframe, pharmacies reached 28% more individuals than community-based agencies (Table 1).

Figure 1. Individuals Receiving Naloxone by Source and Timeframe, Rhode Island, January 1, 2019–March 31, 2022.

Naloxone-distribution events more frequently resulted in distribution to females in both community (50.5%) and pharmacy (56.9%) settings and males in the hospital setting (70.6%, Table 1). The largest proportion of individuals receiving pharmacy-dispensed naloxone were aged 55 to 64 (20.1%), while those receiving naloxone from community agencies and hospitals were aged 25 to 34 (24.6% and 35.0% respectively). Individuals receiving pharmacy-dispensed naloxone used mainly public insurance for payment, with more individuals using Medicaid (31.4%) than Medicare (17.7%). Individuals receiving naloxone from a community-based agency or hospital were mainly Non-Hispanic White (60.1% and 57.3% respectively). For all naloxone sources, individuals most frequently resided in Providence.

DISCUSSION
Over time, Rhode Island’s naloxone distribution has shifted from being driven by pharmacies to a mix of pharmacy and community agency involvement. Individuals most often receiving naloxone from these sources do not always align with individuals at highest risk for experiencing a fatal opioid overdose. For opioid overdose deaths occurring in Rhode Island from 2019 to 2021, decedents were most often male (72%), aged 25–34 (26%), non-Hispanic White (76%), and Providence residents (24%). Though overlap exists between age, race, and residence for those most impacted by fatal overdose and those targeted by naloxone distribution by pharmacies or community agencies, there is a noticeable

Table 1. Characteristics of Individuals Receiving Naloxone at Each Naloxone Distribution by Source, Rhode Island, January 1, 2019–March 31, 2022

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmacy-dispensed (%)</th>
<th>Community-based agency (%)</th>
<th>Hospital-dispensed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Individuals Receiving Naloxone</td>
<td>37,118 (56.9%)</td>
<td>28,897 (45.2%)</td>
<td>2,058 (3.6%)</td>
</tr>
</tbody>
</table>

Recipient Gender

<table>
<thead>
<tr>
<th>Recipient Gender</th>
<th>Pharmacy-dispensed (%)</th>
<th>Community-based agency (%)</th>
<th>Hospital-dispensed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>21,113 (56.9%)</td>
<td>14,603 (40.5%)</td>
<td>605 (17.6%)</td>
</tr>
<tr>
<td>Male</td>
<td>16,000 (43.1%)</td>
<td>13,072 (45.2%)</td>
<td>1,452 (70.6%)</td>
</tr>
<tr>
<td>Transgender</td>
<td>n/a</td>
<td>104 (0.4%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Non-Binary</td>
<td>n/a</td>
<td>152 (0.5%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Not Listed</td>
<td>n/a</td>
<td>121 (0.4%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Multiple Selection</td>
<td>n/a</td>
<td>98 (0.3%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (0%)</td>
<td>747 (2.6%)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Recipient Age Group

<table>
<thead>
<tr>
<th>Recipient Age Group</th>
<th>Pharmacy-dispensed (%)</th>
<th>Community-based agency (%)</th>
<th>Hospital-dispensed (%)</th>
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</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>503 (1.4%)</td>
<td>132 (0.5%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>18–24</td>
<td>1,571 (4.2%)</td>
<td>3,377 (11.7%)</td>
<td>300 (14.6%)</td>
</tr>
<tr>
<td>25–34</td>
<td>5,695 (15.3%)</td>
<td>7,117 (24.6%)</td>
<td>721 (35.0%)</td>
</tr>
<tr>
<td>35–44</td>
<td>5,941 (16.0%)</td>
<td>6,921 (24.0%)</td>
<td>594 (28.9%)</td>
</tr>
<tr>
<td>45–54</td>
<td>6,561 (17.7%)</td>
<td>5,515 (19.1%)</td>
<td>245 (11.9%)</td>
</tr>
<tr>
<td>55–64</td>
<td>7,476 (20.1%)</td>
<td>3,432 (11.9%)</td>
<td>159 (7.7%)</td>
</tr>
<tr>
<td>65+</td>
<td>5,325 (14.4%)</td>
<td>1,464 (5.1%)</td>
<td>38 (1.9%)</td>
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<td>4,046 (10.9%)</td>
<td>939 (3.3%)</td>
<td>0 (0%)</td>
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Insurance

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<tr>
<th>Insurance</th>
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<th>Hospital-dispensed (%)</th>
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</thead>
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<td>Medicare</td>
<td>6,585 (17.7%)</td>
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<tr>
<td>Medicaid</td>
<td>11,658 (31.4%)</td>
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<td>Private Insurance</td>
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<td>n/a</td>
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<td>Worker’s Compensation</td>
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<td>n/a</td>
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<tr>
<td>Unknown</td>
<td>997 (2.7%)</td>
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<td>n/a</td>
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</table>

Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Pharmacy-dispensed (%)</th>
<th>Community-based agency (%)</th>
<th>Hospital-dispensed (%)</th>
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</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>n/a</td>
<td>2,929 (10.1%)</td>
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<td>Non-Hispanic White</td>
<td>n/a</td>
<td>17,378 (60.1%)</td>
<td>1,180 (57.3%)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>n/a</td>
<td>1,815 (6.3%)</td>
<td>153 (7.4%)</td>
</tr>
<tr>
<td>Non-Hispanic Other</td>
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<td>1,100 (3.8%)</td>
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<tr>
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<td>n/a</td>
<td>5,675 (19.6%)</td>
<td>455 (22.1%)</td>
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</table>

Resident Municipality

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<th>Pharmacy-dispensed (%)</th>
<th>Community-based agency (%)</th>
<th>Hospital-dispensed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providence</td>
<td>6,276 (16.9%)</td>
<td>7,511 (26.0%)</td>
<td>590 (28.7%)</td>
</tr>
<tr>
<td>Pawtucket</td>
<td>2,687 (7.2%)</td>
<td>2,422 (8.4%)</td>
<td>190 (9.2%)</td>
</tr>
<tr>
<td>Woonsocket</td>
<td>1,907 (5.1%)</td>
<td>2,142 (7.4%)</td>
<td>158 (7.7%)</td>
</tr>
<tr>
<td>Cranston</td>
<td>3,747 (10.1%)</td>
<td>980 (3.4%)</td>
<td>117 (5.7%)</td>
</tr>
<tr>
<td>Warwick</td>
<td>3,090 (8.3%)</td>
<td>1,455 (5.0%)</td>
<td>83 (4.0%)</td>
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<tr>
<td>Out of state</td>
<td>1,429 (3.9%)</td>
<td>1,236 (4.3%)</td>
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</tr>
<tr>
<td>East Providence</td>
<td>1,578 (4.3%)</td>
<td>586 (2.0%)</td>
<td>86 (4.2%)</td>
</tr>
<tr>
<td>All Other RI municipalities</td>
<td>16,396 (44.2%)</td>
<td>9,685 (33.5%)</td>
<td>585 (28.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (0.0%)</td>
<td>2,880 (10.0%)</td>
<td>45 (2.2%)</td>
</tr>
</tbody>
</table>
disparity in the proportion of males experiencing a fatal opioid overdose and males receiving naloxone for overdose reversal. Hospital-dispensed naloxone demographics most closely overlap with those of opioid overdose deaths.

Age-group distributions among naloxone recipients varied. Individuals receiving pharmacy-dispensed naloxone were more often aged 55 to 64 [20.1%], while those receiving community and hospital-dispensed naloxone were more often aged 25 to 44 [24.6% and 35.0% respectively]. This disparity may be due to differences in the populations utilizing each resource. Pharmacy-dispensed naloxone is more accessible to individuals who have established connections to the healthcare system. These individuals generally have active health insurance, may be taking provider-prescribed opioids, or may be in treatment for opioid use disorder. Older individuals are more likely to have an opioid prescription, which would include mandated naloxone co-prescriptions provided to that age group. This may contribute to age-group distribution differences between the naloxone sources. Those who are underinsured or disconnected from the healthcare system may have multiple situational and financial barriers against obtaining naloxone from a pharmacy. These individuals may alternatively seek services and resources from agencies in their community, including no-cost naloxone, or when seen at a hospital for a non-fatal overdose.

In more recent years, community distribution efforts also shifted from community trainings to targeting high-risk individuals and received a significant increase in funding and resources. Although the increase in community distribution began prior to the start of this campaign, starting in January 2021, the 10,000 Chances initiative aimed to distribute 10,000 naloxone kits and highlighted the demand for harm-reduction materials distributed in community settings. Most distribution from this initiative occurred from January to June 2021. Despite having a one-time funding source, this initiative’s success led to the allocation of additional resources to meet naloxone demand, and therefore a sustained increase in community naloxone distribution. As a result of planning and implementing the 10,000 Chances initiative, there is increased capacity to coordinate the naloxone procurement, request, and distribution process, which has allowed RIDOH to conduct analyses on naloxone distribution which were not possible prior to project implementation. This increased coordination and streamlining of processes, including setting up standard operating procedures, will allow for the anticipated 50,000 kits from the recent opioid settlement to be more easily distributed. Changes in pharmacy distribution were not apparent in the timeframe examined, likely due to the naloxone co-prescription regulation that went into effect in 2018.

Limitations include the inability to compare race and ethnicity groups, along with insurance type and more specific gender categories, among all recipients. Despite being a requirement for community agencies receiving state-sponsored naloxone to enter distribution information, the dataset may not capture every kit distributed, which may underestimate distribution. We also may not capture individuals that receive naloxone from non-RIDOH sources. Since the PDMP only captures prescriptions that are filled rather than all that are prescribed, we were unable to determine which individuals received naloxone as a result of co-prescribing regulations.

Although demographic information allows us to describe individuals accessing naloxone via different sources, further analyses should be conducted to provide more context for distribution. If funding becomes available, qualitative information on why individuals used a specific source to obtain naloxone should be gathered to further describe individuals using each source and guide future distribution decisions. The population receiving pharmacy-dispensed naloxone could be further examined to determine whether disparities exist among individuals who fill standing order prescriptions rather than obtaining a naloxone prescription from a provider. Additionally, information on naloxone utilization for previous overdoses contained in the community naloxone dataset could provide insight as to whether the observed difference in females receiving more naloxone is due to females administering naloxone as bystanders during an overdose. The information on gender contained in this dataset may also help further describe how community-based agencies are reaching high-risk populations.

As the number of fatal overdoses in Rhode Island continues to rise, it is important to understand who is accessing naloxone and what resources they are utilizing to better understand the distribution approaches needed to reach different populations. With the recent opioid settlement bringing approximately 50,000 naloxone kits a year into the state over the next 10 years, there will be a need to use naloxone distribution data, along with overdose morbidity and mortality data, to guide distribution decisions to ensure naloxone is reaching the appropriate individuals. This information can be used to guide future overdose prevention efforts and resource allocation, particularly with the recent implementation of new state regulations surrounding harm reduction, and plans to develop Rhode Island’s first harm reduction center.

References


Acknowledgments
Thanks to Benjamin Hallowell, PhD, and Jennifer Koziol for their assistance and feedback.

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Heidi Weidele, MPH, is a Public Health Epidemiologist for the Substance Use Epidemiology Program, RIDOH.
Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

<table>
<thead>
<tr>
<th>VITAL EVENTS</th>
<th>JANUARY 2022</th>
<th>12 MONTHS ENDING WITH JANUARY 2022</th>
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<td>Live Births</td>
<td>892</td>
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<tr>
<td>Deaths</td>
<td>1238</td>
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<tr>
<td>Infant Deaths</td>
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<td>Neonatal Deaths</td>
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<tr>
<td>Marriages</td>
<td>206</td>
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<td>Divorces</td>
<td>175</td>
<td>2,865</td>
</tr>
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</table>

Rates (b) per 100,000 estimated population
* Rates per 1,000 estimated population
# Rates per 1,000 live births

<table>
<thead>
<tr>
<th>Underlying Cause of Death Category</th>
<th>JULY 2021</th>
<th>12 MONTHS ENDING WITH JULY 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the Heart</td>
<td>171</td>
<td>2,358</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>187</td>
<td>2,161</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>37</td>
<td>427</td>
</tr>
<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>82</td>
<td>1,021</td>
</tr>
<tr>
<td>COPD</td>
<td>28</td>
<td>374</td>
</tr>
</tbody>
</table>

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,097,379 for 2020 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.
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4 under 40

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Working for You: RIMS advocacy activities

August 2, Tuesday
RIMS Physician Health Committee (PHC):
Herbert Rakatansky, MD, Chair
American Medical Association (AMA)
State Advocacy Conference in Stowe, VT

August 3, Wednesday
AMA State Advocacy Conference in Stowe, VT

August 4, Thursday
AMA State Advocacy Conference in Stowe, VT
Meeting with Blue Cross & Blue Shield of Rhode Island (BCBSRI):
Elizabeth Lange, MD, President;
Thomas A. Bledsoe, MD, President-elect

August 10, Wednesday
Governor’s Overdose Task Force (GOTF):
Racial Equity Work Group
Governor’s Overdose Intervention and Prevention Task Force:
Sarah Fessler, MD, RIMS Past President

August 11, Thursday
AMA Federation Health Equity Exchange

August 15, Monday
Office of the Health Insurance Commissioner (OHIC) Measure Alignment meeting:
Peter Hollmann, MD, RIMS Past President

August 16, Tuesday
National Government Services
Key Stakeholder meeting
Rhode Island Health Workforce Planning:
Health & Human Service Partnerships with Higher Education
OHIC Health Insurance Advisory Committee (HIAC):
Catherine A. Cummings, MD, RIMS Past President

August 20, Tuesday
Office of the Health Insurance Commissioner (OHIC) Measure Alignment meeting:
Peter Hollmann, MD, RIMS Past President
American Medical Association Advocacy meeting

August 23, Tuesday
AMA Federation Health Equity Exchange

August 24, Wednesday
Rhode Island Health Workforce Planning:
Health Workforce Data Collection & Analytics Workgroup
RIMS Finance Committee meeting

August 25, Thursday
RIMS Climate Change and Health Committee

August 29, Monday
Office of the Health Insurance Commissioner (OHIC) Measure Alignment meeting:
Peter Hollmann, MD, RIMS Past President

August 30, Tuesday
Rhode Island Health Workforce Planning:
Health Career Pathways & Pipelines Workgroup
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In 2022 to date, more than 30,000 unique viewers from 110 countries have read articles in the Rhode Island Medical Journal or researched topics in its archives.

Top 10 countries:
1. US
2. Canada
3. UK
4. Australia
5. India
6. China
7. Germany
8. Italy
9. Brazil
10. Spain

BODEGA, CALIFORNIA

Associate Editor Kenneth S. Korr, MD, checks out the latest issue of RIMJ, standing in front of the historic Potter School in the town of Bodega, CA, where the scene of children fleeing the school in the Alfred Hitchcock horror/thriller, “The Birds,” was filmed. The plot of the 1963 film revolves around a series of violent and mysterious bird attacks against residents in the coastal California town of Bodega Bay, a short distance from the town of Bodega. The 1873 schoolhouse was condemned and vacant prior to the filming. The building has been restored and is now a private home.

Bodega Bay Harbor with Bodega Head in the distance, a rocky granite promontory overlooking the Pacific Ocean, where Tippi Hedren is shown in the initial scenes in the film rowing a boat to drop off the lovebirds at the Brenner Farm. Today, a marina, fishing pier, and seaside eateries dot the landscape. (PHOTOS BY MARY KORR)

The original film release poster advertising “The Birds,” produced and directed by Alfred Hitchcock for Universal Studios. The screenplay was written by Evan Hunter and based loosely on a novella by Daphne Du Maurier. In 2016, the film was deemed “culturally, historically, or aesthetically significant” by the United States Library of Congress, and selected for preservation in its National Film Registry. (CREATIVE COMMONS IN THE PUBLIC DOMAIN)
‘I’ll Never Be Your Beast of Burden’:
Physician Burnout and Moral Injury

WILLIAM D. BINDER, MD

It was a typically busy Wednesday night. We had 22 people in the waiting room, with admitted patients boarding in the emergency department (ED) due to difficulties with bed availability and staffing. At 3:40 a.m. an 80-year-old woman arrived from a skilled nursing facility after staff found her unresponsive. Emergency Medical Services (EMS) discovered her to be pulseless and in asystole, and after 4 rounds of epinephrine in the field, she arrived in room 2 of my ED. As she was a “full code,” I intubated her and initiated resuscitation measures. A bedside echo revealed cardiac standstill and after 2 more rounds of epinephrine, calcium chloride, and bicarbonate infusion, she was pronounced dead. After a moment of silence, I attempted to contact family members, called the medical examiner and the organ bank, and began entering data required by our electronic health record (EHR).

I next turned my attention toward the completion of the death certificate. On paper, the death certificate takes about 4 minutes to complete and is self-explanatory. However, more than a year ago, the Rhode Island Department of Health instituted and now mandates use of the Rhode Island Vital Events Registration System (RIVERS), an electronic web-based application from Genesis Systems, Inc., to register and record deaths. RIVERS required a 90-minute tutorial, which I dutifully undertook, reviewed, and forgot. Deaths in the ED are high-acuity, but fortunately, low-frequency events, and I had never completed an electronic death certificate previously. I bumbled my way through the program, and after 65 minutes I completed the information and certified the patient’s death. My active patients waited, and during that hour I received 4 “new” patients, all of whom had been waiting 3–4 hours to be seen by a physician.

Clerical storm halts funeral plans
Meanwhile, a storm was brewing. I usually sleep after working an overnight shift and I awoke to a torrent of secure chat messages and texts from the medical records department and the director of the ED. The family and funeral home could not move the patient’s body until I completed the certificate, which I naively thought I had done. Panicked, I contacted colleague after colleague asking questions about the program, but none could help – they said the program was so opaque and obtuse that most had never completed it successfully. Over the next 2½ days I spent many waking hours attempting to rectify the problem. Thankfully, the body was taken by the funeral home despite the missing “paperwork,” but the messages and calls continued. Finally, on Saturday afternoon, a troubleshooter from the help desk at Genesis Systems called me on my cell phone. My help desk savior was able to efficiently walk me through the program over the next 15 minutes until we came to a road block. I had answered one question “wrong” about my office location. My office is on Claverick Street with Brown Emergency Medicine – but the program was looking for a different answer. It wanted the hospital name. Because of this error, my help desk friend was unable to complete the program, and so, after 3 days and rising tensions, it was referred to someone at the state level, who sent me an automatic reply that he was unavailable. What was formerly a 4-minute process had dragged out over 3 calendar days.

I worked the entire weekend after this event – it is the nature of emergency medicine – and so the following Monday I took time to catch up on notes and “paperwork.” I completed about 50 charts, and I attempted to renew my Massachusetts Physician License for $600. All went well until I found that I needed to complete an hour of mandatory CME on Alzheimer’s disease. My choices were to spend $149 to take the Massachusetts Medical Society course, $49 for another course, or I could register for Medscape and take its course. I did the latter. The courses were fairly meaningless to my practice – no one is suffering from acute Alzheimer’s in the ED – but I like to learn, and so, after an hour, I was able to renew my license, which took about 5 minutes. What struck me was that after each mini course (two 15-minute courses, followed by a 30-minute course), I had to complete three separate 16-question modules regarding the value of the courses. The questionnaires on satisfaction were 8x longer than the course questions! Fortunately, I had another hour left in my morning so I could complete the learning modules on corporate compliance and HIPAA [for the nth time] mandated by my health care system prior to going for a run on my day off.

I am a relatively resilient physician. I have completed two residencies, survived [thus far] three pandemics (AIDS, H1N1, and SARS-CoV-2), taken care of about 100,000 ED patients during my career at the Massachusetts General Hospital [MGH] and Brown, and I have endured multiple
EHR iterations. I have made errors and have been insightful; I have been prickly, and I have been magnanimous – in short, I have been human. And as a human, and as a physician, I feel exasperated by a chaotic system that purports to revolve around patient safety, but impedes it by extracting every ounce of my creativity and energy. There is a reason the literature on physician burnout has exploded over the past several years, and even the United States Surgeon General Vivek Murthy, MD, has recognized that burnout is a public health care crisis.1

Defining burnout and moral injury
Burnout has been defined as “a syndrome of emotional exhaustion, loss of meaning in work, feelings of ineffectiveness, and a tendency to view people as objects rather than as human beings.”2 But the usual ingredients associated with burnout – time spent on non-clinical tasks, information technology demands, loss of autonomy, organizational/systems factors – do not entirely explain my exasperation.3,4 I, along with many colleagues, work in a system that contributes to what is now defined as moral injury, a precursor to burnout. First used to describe veterans returning from the Vietnam War, moral injury has been extended to the health care field to help further explain and refine causes of burnout.1 Burnout suggests individual deficit. Moral injury stems from deficiencies in the system.5 As Dean notes, “Moral injury is the consequence of the ever-present double binds in health care: Do we take care of our patient, the hospital, the insurer, the EMR, the health care system, or our productivity metrics first?”6 The answer should be straightforward [the patient!], but unfortunately, physicians and other health care workers are pulled in competing directions.

I am a late-career physician and the data suggests that I am less vulnerable to the factors associated with burnout.5 I still love seeing patients, interacting with colleagues, and uncovering the daily puzzles presented to me. But I am not a beast of burden, to be saddled with every ancillary project that detracts from my life, and adds limited value or benefit to my practice. Like Howard Beale from Paddy Chayefsky’s brilliant and caustic screenplay “Network” (for those under 50, you may wish to YouTube this), I want to scream, “I am mad as hell, and I am not going to take it anymore.”

But I can’t – I need to complete the Med-IQ modules for our Quality and Safety Department so I can participate in my department’s risk mitigation program. ∗

References

Author
William D. Binder, MD, Associate Professor of Emergency Medicine, Warren Alpert Medical School of Brown University; Editor-in-Chief, Rhode Island Medical Journal.

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American Lung Association seeks grant applications from RI researchers

Organization opens application process for 2023–2024 awards and grants funding

PROVIDENCE – The American Lung Association in Rhode Island recently announced the start of its 2023–2024 research awards and grants cycle. The organization is now accepting research grant applications from researchers here in Rhode Island and across the nation with the potential to improve prevention, detection and treatment options for all lung diseases including lung cancer.

“Here in Rhode Island, we have wonderful research institutions and leading-edge researchers,” said DANIEL FITZGERALD, Director of Advocacy for the American Lung Association in Rhode Island. “The Lung Association is committed to supporting the best scientific minds to help develop solutions to alleviate the burden of lung disease. We encourage innovative researchers in Rhode Island to apply for these grants.”

Research projects funded by the Lung Association are carefully selected through rigorous scientific review and awardees represent the investigation of a wide range of complex issues to reduce the suffering and burden of lung disease.

Below is a list of currently available research funding opportunities:

- **COVID-19 & Respiratory Virus Research Award:**
  $100,000 per year for up to two years
  This award is intended to support investigators who have the ability to advance our knowledge of COVID-19 and other novel respiratory viruses with pandemic potential.
  Successful applicants have evidence of ongoing excellence and productivity in a related field.

- **Lung Cancer Discovery Award:**
  $100,000 per year for up to two years
  Intended to support independent investigators conducting clinical, laboratory, epidemiological or any groundbreaking project aimed at revolutionizing our current understanding of lung cancer and improving diagnostic, clinical and treatment methods. A Letter of Intent (LOI) is required for this award.

- **Allergic Respiratory Diseases Award:**
  $75,000 per year for up to two years
  A long-standing joint effort between the American Lung Association and the American Academy of Allergy, Asthma & Immunology to encourage and support early-stage investigators with a primary faculty appointment in an allergy/immunology division or section, to conduct research into advancing the understanding of allergic respiratory disease.

- **Innovation Award:**
  $75,000 per year for up to two years
  This award will support promising independent investigators who are leveraging their existing body of work to conduct basic science, behavioral, clinical or translational research for lung health.

- **Catalyst Award:**
  $50,000 per year for up to two years
  This award champions the next generation of scientists who are ascending toward independence by supporting mentored investigators who are conducting basic science, behavioral, clinical or translational research into lung health.

- **Public Policy Research Award:**
  $50,000 per year for up to two years
  This mechanism is designed to help stimulate and inform important public policy debates around healthy air and lung disease. This award supports research on and evaluation of existing public policy and programs, as well as projects that inject innovative ideas into public policies impacting lung health.

- **Dalsemer Award:**
  $50,000 per year for up to two years
  This is a mentored award meant to provide seed monies to junior investigators for researching the mechanisms and biology of interstitial lung disease.

For more information about the active research funding opportunities, visit Lung.org/awards.
Lung cancer is the leading cause of cancer deaths in Rhode Island

PROVIDENCE – Here in Rhode Island and across the nation, lung cancer is the leading cause of cancer deaths; however, survey data released August 1 show that only 40% of Americans are concerned that they might get lung cancer and only about one in five have talked to their doctor about their risk for the disease. On World Lung Cancer Day, the American Lung Association’s LUNG FORCE initiative released the 2022 Lung Health Barometer, a national survey that examines awareness, attitudes and beliefs about lung cancer.

In Rhode Island, it is estimated that 980 people will be diagnosed with lung cancer in 2022, and 480 people will die from the disease. But there is hope. The lung cancer survival rate has risen substantially, and awareness of this deadly disease has steadily increased. Greater awareness of lung cancer is key to securing research funding, encouraging lung cancer screening, reducing stigma around this disease, and ultimately, saving lives.

“One of the most impactful things we can do in Rhode Island is to raise awareness about lifesaving lung cancer screening. Currently, only 6% of residents at high risk for lung cancer have received a low-dose CT screen lung cancer screening,” said DANIEL FITZGERALD, Director of Advocacy at the Lung Association in Rhode Island. “Lung cancer screening is key to early diagnosis, and early diagnosis saves lives.”

While awareness about lung cancer screening is still low, there has been significant work done recently to increase eligibility. Last year, the U.S. Preventive Services Task Force expanded the guidelines for screening to include individuals ages 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. This nearly doubled the number of individuals eligible for screening and has the potential to save significantly more lives than previous guidelines.

The 2022 Lung Health Barometer surveyed 4,000 Americans nationwide about lung cancer. Key findings show that:

- Only about one in four respondents [26%] were aware that the lung cancer survival rate increased by over 30% in the past ten years.
- 73% of adults have not spoken with their doctor about their risk for lung cancer and only 40% are concerned they might get the disease.
- Only 29% of Americans know that lung cancer is the leading cancer killer in the U.S.
- Nearly 70% of respondents were not familiar with the availability of lung cancer screening for early detection of the disease.

This is the seventh year of the Lung Health Barometer, which is conducted by the Lung Association’s LUNG FORCE initiative. LUNG FORCE unites those impacted by lung cancer and their caregivers across the country to stand together against lung cancer.

Alzheimer’s Association global workgroup releases recommendations on use of blood biomarkers (BBMs)

CHICAGO AND SAN DIEGO – Alzheimer’s disease blood biomarkers (BBMs) may revolutionize the diagnosis of Alzheimer’s in the future, but are not yet ready for widespread use, according to a newly-published article by leading international clinicians and researchers convened by the Alzheimer’s Association. At the same time, they are important and valuable for current research trials and cautious initial use in specialized memory clinics.

“The Alzheimer’s Association Appropriate Use Recommendations for Blood Biomarkers in Alzheimer’s Disease,” by OSKAR HANSSON, MD, PhD, et al, is published online by Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association. The recommendations were reported in July at the Alzheimer’s Association International Conference® [AAIC®] 2022 in San Diego and online.

The recommendations were made by a global workgroup convened by the Alzheimer’s Association, which included leading Alzheimer’s disease researcher STEPHEN SLOWWAY, MD, MS, one of the article’s authors. Dr. Salloway is founder of the Memory and Aging Program at Butler Hospital and is also the Martin M. Zucker Professor of Psychiatry and Human Behavior, Professor of Neurology, and Associate Director of the Center for Alzheimer’s Disease Research at Brown University.

“Blood-based markers show promise for improving, and possibly even redefining, the diagnostic work-up for Alzheimer’s,” said MARIA C. CARRILLO, PhD, Alzheimer’s Association chief science officer and a co-author of the article. “Remarkable progress has been made, but additional data are needed before BBMs can be used as a stand-alone test for diagnosis, and before considering broad use in primary care settings.”

“In this article, the expert workgroup clearly defines both short- and long-term research priorities needed to fill significant knowledge gaps that still exist, such as how well these blood-based markers work in diverse communities and in those living with multiple health conditions,” Dr. Carrillo added. “Also included are consensus appropriate use recommendations for use of BBMs in the clinic and in research trials.”

“Blood-based biomarkers for Alzheimer’s are already improving the design of clinical trials, and they are very likely to revolutionize the diagnosis of Alzheimer’s in the future,” said Dr. Hansson, director of the Center for Neurodegenerative Diseases at Lund University and Skane University Hospital, Malmo,
Sweden, and first author on the newly published article. “That said, the implementation of such markers in trials and practice must be done in a careful and controlled way so as not to accidentally cause more harm than good. Much more research is needed before widespread clinical use of BBMs.”

Defining the need
According to the workgroup, about 25–30% of patients with a clinical diagnosis of Alzheimer’s dementia are misdiagnosed when assessed at specialized dementia clinics, and the accuracy of clinical diagnosis is similar or even lower for other dementias, including frontotemporal dementia, dementia with Lewy bodies and vascular dementia. In fact, in most countries, most patients with cognitive or behavioral symptoms are managed in primary care where the misdiagnosis is even higher. The problem is especially acute in the earliest stages of the disease.

“There is a great global need for accurate BBM-based diagnostic and prognostic algorithms that can substantially improve the accuracy of a diagnostic work-up of Alzheimer’s, particularly in the early stages of the disease,” said REISA SPERLING, MD, professor of Neurology at Harvard Medical School and director of the Center for Alzheimer Research and Treatment at Brigham and Women’s Hospital and Massachusetts General Hospital, and a co-author of the article.

The established CSF and PET measures have excellent diagnostic properties, but are less useful outside very specialized clinics due to limited accessibility, invasiveness (e.g., CSF measures require a lumbar puncture, and PET requires infusion of stable isotopes and exposure to radiation) and high costs. This precludes use of CSF and PET biomarkers in most primary and secondary care settings worldwide.

According to the article, BBMs show “great promise” – especially markers for Alzheimer’s-related brain changes related to nerve cell damage/death, and tau and beta amyloid accumulation – for “future use in both clinical practice and trials. However, few prospective studies have investigated the implementation of such BBMs in more heterogeneous populations.”

Not ready for “prime time”
The workgroup points out that no studies have extensively evaluated BBMs for neurodegenerative diseases in primary care, and calls for “well-performed BBM studies in diverse primary care populations.” Such studies should also evaluate the impact of BBMs on diagnostic accuracy and change in patient management.

In addition, use of BBMs for general population risk screening and as direct-to-consumer risk tests are not recommended.

The workgroup also says that BBMs should not yet be used as primary endpoints in pivotal treatment trials. However, this does not preclude the use of certain BBMs for decision making in clinical trials with adaptive design, where they could be used to inform decisions on continuing a trial or not.

Many current uses
There are current uses for Alzheimer’s BBMs, according to the workgroup. For example, they “recommend use of BBMs as [pre]-screeners to identify individuals likely to have Alzheimer’s pathological changes for inclusion in trials evaluating disease-modifying therapies, provided Alzheimer’s status is confirmed with positron emission tomography [PET] or cerebrospinal fluid [CSF] testing.”

BBMs can be used as exploratory outcomes in most clinical trials in Alzheimer’s and other neurodegenerative dementias. In non-Alzheimer’s trials, BBMs can be used to identify patients who likely have Alzheimer’s-related brain changes, if that is a condition of exclusion from the study.

Dr. Salloway said that further development and implementation of BBMs alongside further development of potential treatments for Alzheimer’s disease, could lead to an end to Alzheimer’s disease as we know it today. “The more we learn from Alzheimer’s research, the more it has become clear that prevention and early intervention are the keys to defeating this disease.” We’re likely decades away from having the knowledge and technology to try and reverse the disease once it has become advanced, if that ever becomes possible at all. But the ability to identify it in its earliest stages and develop disease-modifying drugs that prevent life-altering symptoms may be closer than we think.”
Ortho RI Surgeon Michael Bradley, MD, performs first reverse shoulder replacement surgery using FX V135™ implant in US

WAKEFIELD – Ortho Rhode Island surgeon MICHAEL P. BRADLEY, MD, MBA, MS, completed a reverse shoulder arthroplasty, more commonly known as a reverse shoulder replacement, using the FX V135™ implant, at South County Hospital. This was the first surgery to employ this technology in the United States. The landmark procedure was performed in late July at the Center for Advanced Orthopedic Surgery, a partnership between Ortho Rhode Island and South County Health. The surgery is part of Ortho Rhode Island’s mission to pioneer orthopedic treatments that make care more patient-centered.

“Procedures that preserve bone are becoming a high priority to patients. That’s why I believe the FX V135™ implant is a good option to consider for anyone in need of reverse shoulder replacement,” Dr. Bradley said.

The new FX V135™ shoulder system includes a mini stem humeral component that can be configured for both anatomical and reverse shoulder replacements and offers humeral head components with variable head heights to allow surgeons more flexibility to best match the patients’ anatomy in the anatomic configuration.

In addition to performing a milestone surgery with the FX V135™, Dr. Bradley is a member of the device’s design team. He worked closely with FX Solutions, a global leader in shoulder arthroplasty, to help create an implant that would meet patients’ needs. “The FX V135™ was designed to allow surgeons to tailor our system to the patient—rather than the patient to our system,” said BAPTISTE MARTIN, CEO of FX Solutions.

As President and CEO of Ortho Rhode Island, Dr. Bradley is excited about the way orthopedic innovations like the FX V135™ are improving the patient experience. “Ortho Rhode Island’s role in introducing this technology to the U.S. is another example of our commitment to state-of-the-art care that puts patients first. We are proud to lead the way in bringing innovation to orthopedics,” Dr. Bradley said.

RIH study finds better outcomes for stroke patients triaged directly to Level 1 Stroke Centers

PROVIDENCE – Rhode Island Hospital researchers have found that implementing severity-based field triage leads to faster treatment and less disability for stroke patients. The findings, now published online in the Journal of NeuroInterventional Surgery, show that states that use field-based stroke severity triage as part of their Emergency Medical Systems (EMS) transport protocols give severe stroke patients more rapid access to specially trained neuroendovascular care teams and lifesaving thrombectomy.

In the study, “Long Term Effect of Field Triage on Times to Endovascular Treatment for Emergent Large Vessel Occlusion,” researchers compared stroke patients over two adjacent states over a 5½ year span. Both states were served by a single Level 1 [Comprehensive] stroke center. After matching the patients from the two regions based on distance to the Level 1 center, time to treatment decreased by 55 minutes after implementation of severity-based triage. In contrast, there was no change in time to treatment in the adjacent region with traditional EMS protocols over 5½ years, despite extensive efforts to improve workflow at referring hospitals. As a result, clinical outcomes at 90 days were significantly better in those patients who resided in the state with severity-based triage, compared with traditional EMS protocols.

“The time lost in transfer from the nearest hospital to the best-equipped facility clearly jeopardizes a patient’s chance of recovery,” said MAHESH JAYARAMAN, MD, lead author of the study, a neurointerventional radiologist and Professor of Diagnostic Imaging, Neurology and Neurosurgery at Brown University, and Director of the Neurovascular Center at Rhode Island Hospital. “We hope this research persuades state governments to take a close look at their stroke care protocols and implement changes to improve triage and transport.”

Link to article: https://pubmed.ncbi.nlm.nih.gov/35896319/
Legislative investments enacted in state’s behavioral health care system

WARWICK – New legislative initiatives and budget investments aimed at strengthening the state’s behavioral health care system included in the budget signed by Governor DAN MCKEE in June are:

• $30 million to begin the transition to the Certified Community Behavioral Health Clinics (CCBHC) model of community-based mental health care which will improve access to care and the quality of care
• $4.2 million to create a Mental Health Treatment Court
• $8 million to build a 25-bed short stay unit at Butler Hospital to provide behavioral health care services, crisis intervention, and other related services
• $1.9 million to support the 9-8-8 Suicide Prevention and Mental Health Crisis Hotline
• $1 million for the design and engineering of suicide barriers on the state’s four tallest bridges

These investments are in addition to $170 million that the state is investing in Eleanor Slater Hospital over the next several years to pay for renovations, new construction, and an electronic medical records system.

“We all know that behavioral health care is an essential component of our health care system, and these investments will result in more support and better results,” said Governor McKee. “The 988 hotline and the transition to the CCBHC model of community-based health care will help us reach and help more people. In the long run, this will reduce the need for longer-term hospitalizations. At the same time, having a Mental Health Court will divert people away from the criminal justice system and connect them with community-based treatment services, and adding barriers to our largest bridges will help to save lives.”

RICHARD CHAREST, Director of the Department of Behavioral Healthcare, Developmental Disabilities and Hospitals, said the transition to a CCBHC model is critical. “CCBHCs offer mental health and substance use treatment services, including 24/7 mobile crisis response, which enables the team to engage clients where they are. This reduces the transportation barrier when someone is in crisis. CCBHCs also provide a comprehensive range of services for anyone who needs help with behavioral health or substance use conditions.”

Director Charest noted that Rhode Island has consistently had the best in-state call response rate for the suicide prevention line, and that trend appears to be continuing with the new 988 suicide and crisis prevention lifeline.

The Governor also ceremonially signed the following bills related to behavioral health:

• H6667B [Ranglin-Vassell] and S2556A [Cano]: This legislation directs the commissioner of elementary and secondary education to establish a trauma-informed schools implementation plan to support to support the academic, behavioral, social and emotional needs of all students.
• H7501 [McNamara] and S2605 [DiMario]: This legislation increases public access to professional psychological services by allowing for telepsychological practice across state lines as well as temporary in-person, face-to-face services in a state where the psychologist is not licensed to practice psychology.

“Each and every one of us experiences trauma at some point in our lives, some more than others, and the trauma we experience as children can shape our lives forever. The difference that determines whether we are able to be resilient and recover is whether we are supported by those in our community,” said Rep. MARCIA RANGLIN-VASSELL [D-Dist. 5, Providence], who works as a teacher at E-Cubed Academy in Providence. “In schools, teachers like myself see kids suffering every day from the trauma they have experienced, particularly during the pandemic the last couple of years. The mental-emotional needs of our children need to be met with care, and teachers and staff need resources to know how they can respond in ways that are helpful.”

“As lawmakers, we have been working on creative ways to reduce the barriers providers face in obtaining a license to practice,” said Rep. JOSEPH M. MCNAMARA [D-Dist. 19, Warwick, Cranston]. “The National Institute of Mental Health estimates that one in four adults, or 60 million people, experience mental illness. This legislation is another creative way to address the shortage of mental health professionals to get all Rhode Islanders the care that they need.”

“Through passage of this legislation, we would be joining 33 other states to allow for telehealth services across state lines in participating states with a universal credential through the compact that maintains high standards of patient protection and care,” said Sen. ALANA M. DIMARIO [D-Dist. 36, Narragansett, North Kingstown]. “Without passage of this bill the temporary COVID waivers allowing this will expire at the end of June, which would leave many Rhode Islanders suddenly without access to their treatment and many providers having to end care for their out of state patients.”
Newport Hospital begins 150th-year celebrations

NEWPORT – Newport Hospital raised a banner in August to officially begin celebrating an upcoming milestone in its history – a century and a half of serving the community. Founded in 1873, the hospital is entering its 150th year of providing top notch medical services to the people of Newport County and beyond.

“Newport Hospital has a culture steeped in history, hospitality, healing, health, and hope,” said Newport Hospital President CRISTA DURAND. “As a community we honor and celebrate this momentous occasion in the hospital’s history, and together we will continue to move Newport Hospital forward for the next 150 years and beyond.”

Over the next year, there will be a series of events to commemorate the hospital’s rich history, and thank the many individuals who have helped make the institution what it is today – a 129-bed award-winning facility offering a wide range of essential, high-quality health care in Rhode Island.

Founded and funded by local residents and its community, Newport Hospital began operation as a 12-bed cottage hospital on donated land. Henry Ledyard, a founding incorporator and trustee, was the hospital’s first president. Over the past century and a half, there have been many noteworthy dates and achievements at Newport Hospital, including:

• In 1893 Newport Hospital completed its first major expansion that added new, well-equipped operating rooms to accommodate advances in surgery and the increase in women who were opting to have their babies in a hospital instead of at home.
• On August 16, 1970, the hospital held a dedication day to open a new expanded main facility (Tower Building); U.S. Senator Claiborne Pell delivered the dedicatory address. Today, this eight-story building is home to the hospital’s ICU, medical/surgical unit, behavioral health unit, Noreen Stonor Drexel Birthing Center, Vanderbilt Rehabilitation Center, Norman Prince Spine Institute, Newport Physical Medicine and Rehabilitation outpatient practice, Vanderbilt wound care center, and Lifespan Cancer Institute.
• In 2000, the hospital opened a new wing and partnered with the nearby Naval Station Newport to offer services to the military.
• The hospital raised $12.5 million through their “Beyond the Building” campaign, which was used to expand and renovate the emergency department, nearly doubling the number of treatment rooms and overall footprint when completed in 2018.
• In 2021 the Vanderbilt Rehabilitation Center at Newport Hospital underwent a transformative expansion, becoming the flagship inpatient rehabilitation center for all of Lifespan.

VA Providence Healthcare System announces ribbon-cutting for new mental health building

PROVIDENCE – The VA Providence Healthcare System (VAPHS) announced a ribbon-cutting for a new mental and behavioral health building to be held on Monday, September 12, 2022, at 10am. The program will take place at the newly constructed facility on the campus of the VAPHS Providence campus 830 Chalkstone Ave.

The new building comprises more than 15,000 square feet of newly constructed space for mental health providers at a cost of more than $14 million dollars. Some of the mental health programs that will be housed in the new facility include:

• Community-Based Employment Services – which provides Veterans treatment for mental health or substance abuse issues with vocational services designed to lead to successful employment.
• Peer Support Program – which trains fellow Veteran who teach goal setting, problem solving, symptom management skills and a variety of other recovery tools.
• Transactional Work Therapy Program – Providing Veteran real work experience through temporary work sites at the VA Providence Healthcare System, Providence campus, among many others.

“Providence is committed to providing state-of-the-art mental health services for the Veterans we serve,” said LAWRENCE CONNELL, VAPHS Director. “This new facility provides a modern setting to provide those services” he said.
Appointments

Kaitlin Lee, MD, joins South County Center for Women’s Health

Wakefield – The South County Medical Group recently announced that Kaitlin R. Lee, MD, FACOG, is now part of Center for Women’s Health where she specializes in obstetrics/gynecology.

Dr. Lee has expertise in providing obstetric and gynecologic care for patients from adolescence through menopause. She brings experience in traditional laparoscopic and abdominal surgery, with additional expertise in vaginal surgery.

Prior to joining South County Health, Dr. Lee provided care for normal and high-risk patients in private practice.

She received her medical degree from University of Illinois College of Medicine and completed her Obstetrics and Gynecology Residency at Dartmouth Hitchcock Medical Center in Lebanon, NH, and is board-certified by the American Board of Obstetrics and Gynecology.

BCBSRI expands physician clinical team

Providence – Blue Cross & Blue Shield of Rhode Island (BCBSRI) has recruited two experienced physicians to serve as senior medical directors.

Louanne Giangreco, MD, an emergency medicine physician and former vice president and chief medical officer of Cayuga Health System in Ithaca, NY, and Gonzalo Paz-Soldán, MD, CPE a pediatrician and former medical director for partner transformation in value-based programs with Horizon Blue Cross Blue Shield of New Jersey.

“Dr. Giangreco and Dr. Paz-Soldán each have outstanding experience as physicians and medical leaders,” said Matthew Collins, MD, MBA, BCBSRI executive vice president and chief medical officer. “With their expertise and diverse backgrounds, they are ideally qualified to lead BCBSRI’s efforts to enhance our members’ experience, advance the quality of the care they receive, address health inequities and improve the well-being of all Rhode Islanders.”

Dr. Giangreco received her medical degree from Albany Medical College in Albany, NY, and completed a residency in emergency medicine at Upstate Medical Center in Syracuse, NY. She is a fellow of the American College of Emergency Physicians.

Prior to her role at Cayuga Health System, Dr. Giangreco was vice president and chief medical officer of healthcare improvement for Excellus Blue Cross Blue Shield and chief medical officer for Five Star Urgent Care, both in Syracuse. She served as an emergency medicine physician at several New York medical centers, including Cayuga Medical Center in Ithaca, Auburn Memorial Hospital in Auburn, United Health Services in Binghamton, and Community General Hospital in Syracuse.

Dr. Paz-Soldán received his medical degree from Yale University School of Medicine and completed his residency in pediatrics at Children’s National Medical Center in Washington, DC. He is board-certified in pediatrics and a fellow of the American Academy of Pediatrics. He is a Certified Physician Executive.

Prior to working for Horizon Blue Cross Blue Shield of New Jersey, Dr. Paz-Soldán served as regional executive medical director for pediatrics at Reliant Medical Group in Worcester, Mass.; medical director for Arlington Pediatric Center at Virginia Hospital Center in Arlington, Va.; medical director for the Inova Pediatric Center at Inova Fairfax Hospital for Children, Falls Church, Va.; and general pediatrician at Virginia Medical Associates, Fairfax, Va., and the University of Maryland Department of Pediatrics, Baltimore, Md. Dr. Paz-Soldán, who speaks Spanish, also worked as a pediatrician in Lima, Peru.

PEOPLE / PLACES

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Kevin Charpentier, MD, named VP SCMG, CMO at South County Health

WAKEFIELD – KEVIN P. CHARPENTIER, MD, has been named Vice President, South County Medical Group and Chief Medical Officer at South County Health. His position on the Executive Leadership Team began July 5, 2022.

Dr. Charpentier was selected by a diverse search committee of physicians, board members, executive leadership and additional key stakeholders based on his outstanding contributions to academic and community medicine, as well as his exemplary leadership demonstrated in similar roles. He was most recently Chief of Surgery at Signature Healthcare, a $381 million organization, headquartered in Brockton, Massachusetts.

A proven leader in healthcare, Dr. Charpentier brings extensive clinical and leadership experience in service line development, network integration, physician recruitment, profit and loss management, regulatory compliance, and clinical and translational research.

Through his leadership, Dr. Charpentier has united disparate hospitals, medical groups, and foundations toward shared visions and common interests developing regional thoracic surgery, urology, minimally invasive foregut surgery, oncology, and medical and surgical programs while facilitating the development of many other medical specialties.

“Dr. Charpentier’s ability to develop, grow, and scale service lines across multiple hospitals while acting as a steward of health system resources and champion of patient safety, quality, and experience made him a standout candidate for South County Health’s Vice President of South County Medical Group and Chief Medical Officer,” said Aaron Robinson, president and CEO of South County Health.

In this executive leadership role, Dr. Charpentier will serve as an expert resource to the medical staff and will work closely with its leaders, South County Medical Group providers, and administrators, under the direction of the president and CEO, to ensure the continued growth and sustainability of the system.

Dr. Charpentier holds a Master of Arts from Brown University. He received his medical degree from Tufts University School of Medicine and is currently completing a Master of Business Administration from the Iseberg School of Management at the University of Massachusetts, Amherst.

Vanzetta James, DNP, MBA named Senior VP of Patient Care Services, Chief Nursing Officer at Miriam

PROVIDENCE – The Miriam Hospital has appointed VANZETTA JAMES, DNP, MBA, as its Senior Vice President of Patient Care Services and Chief Nursing Officer. James comes to The Miriam with over 20 years nursing leadership experience in magnet, teaching, and academic medical centers.

Dr. James most recently served as the Senior Vice President and Chief Nursing officer at University of Maryland Capital Region Health, where she was responsible for the overall nursing practice in the inpatient, emergency and trauma, perioperative, procedural, and ambulatory settings. Her major accomplishments included the implementation of a shared governance structure, a quarterly nursing publication and a successful transition into a new hospital.

“Following a thorough national search, we are pleased and privileged to have Dr. James join us in this important hospital leadership role. With her background, experience, and passion for nursing practice, patient safety, patient experience, quality improvement and evidence-based practice, I am confident she will be a great fit for The Miriam Hospital team,” said MARIA DUCHARME, DNP, RN, NEA-BC, president of The Miriam Hospital.

She earned her Doctor of Nursing Practice degree in leadership from Quinnipiac University in Hamden, CT. She holds a Master of Business Administration from the University of Baltimore, a Master of Science in Health Services Leadership and Management from the University of Maryland School of Nursing in Baltimore, MD, a Bachelor of Science in Nursing from University of Delaware, and an Associate of Science in Nursing from the College of the Virgin Islands. Dr. James is certified in critical care nursing as well as nursing executive practice.

Dr. James is a member of the American Association of Critical Care Nurses, Sigma Theta Tau, and the American Organization for Nursing Leadership.
Recognitions

Emily Miller, MD, named Aspen Institute Fellow

WASHINGTON, DC – The Aspen Institute in August announced its 2022 Aspen Institute Ascend Fellows, 22 leaders from across the United States who are primed to transform systems so that our youngest children and families can thrive. Among the honorees is EMILY MILLER, MD, Associate Professor of Obstetrics and Gynecology at the Warren Alpert Medical School of Brown University and the Division Director of Maternal-Fetal Medicine at Women and Infants Hospital.

The 2022 cohort is focused on mindset and systems change to ensure our youngest children and families thrive. These leaders work across sectors and systems of early learning and care, from connecting mental health and infant-maternal well-being to critical economic supports. In addition, the 2022 cohort includes a commitment to building services and policies designed by and for parents and caregivers to drive national early learning, racial equity, and family well-being in systems of care and well-being as well as solutions and learning from Indigenous wisdom and cultural traditions. The diverse cohort includes Black, Indigenous, Latinx, and other leaders of color focused on eliminating systemic inequities and disparities for young children and families.

“Breaking the cycle of intergenerational poverty starts by changing the trajectory for our youngest children and families in early childhood, and we are honored to have these 22 changemakers committed to making that change happen,” said Anne Mosle, vice president of the Aspen Institute and founder and executive director of Ascend.

Ascend is accelerating its investments in leadership, with a new cohort each year and every other year prioritizing leadership focused on our youngest children and families. The emphasis on our youngest children and families builds on lessons illuminated in Ascend’s recent publication, Toward A More Equitable Tomorrow: A Landscape Analysis of Early Childhood Leadership.

“At the Aspen Institute, we work to understand the lived experiences of those with whom we partner so we can support the systems that are working for the most vulnerable in our society, and change those that are not,” said Dan Porterfield, President and CEO of the Aspen Institute. “Our new 22 Ascend Fellows are leaders who are doing just that – driving change that advances equity for children and families – and we could not be more excited to support them and welcome them into our community.”

In the spirit of radical collaboration and fostering partnerships, these leaders will gather together in person four times over the next 18 months to learn from and with each other. With Ascend and their cohort, Ascend Fellows will develop an action plan that aligns with their organizational goals and individual leadership journeys to advance the north star of intergenerational economic mobility and well-being for children and families. Fellows will also have the opportunity to apply for small grants intended to be catalytic capital to accelerate Fellows’ work where flexible resources could help drive results or meet a critical need.

Arun K. Singh, MD, receives honorary doctorate from Bryant University

SMITHFIELD – ARUN K. SINGH, MD, FLCS, received a Doctor of Humane Letters Honoris Causa from Bryant University and delivered the commencement address to the 47 members of the Physician’s Assistant graduating class of 2022, who earned their Master of Science in Physician Assistant Studies (MSPAS).

Dr. Singh is a Professor of Surgery Emeritus at the Alpert Medical School and has been an adjunct professor at Bryant University’s Physician Assistant program since 2016.

He began practicing at Rhode Island Hospital almost 50 years ago and helped to build a nationally recognized cardiac surgery program there. Dr. Singh performed more than 15,000 heart surgeries and 5,000 related procedures before retiring from active surgery in 2016.

He has authored, edited, and co-edited many books including “Your Heart, My Hands,” which chronicles his life, from his childhood in India to his career and interaction with his patients. [See RIMJ book review: http://rimed.org/rimedicaljournal/2019/02/2019-02-78-book-singh.pdf]

Dr. Singh has received numerous awards, including the Hero at Heart award from The American Heart Association and the lifetime achievement designation from Rhode Island Hospital. He was inducted into the Rhode Island Heritage Hall of Fame in 2017.
Rhode Island Team Hope Walk to take place at Colt State Park on Sept. 25th
Hosted by local chapter of the Huntington’s Disease Society of America (HDSA)

BRISTOL – The Massachusetts and Rhode Island Chapter of the Huntington’s Disease Society of America (HDSA) will host the Rhode Island Team Hope Walk on Sunday, September 25th at 11:00 a.m. at Colt State Park. All proceeds support HDSA’s mission to improve the lives of people affected by Huntington’s disease (HD) and their families.

“Team Hope Walks have always been a favorite HD event of mine,” said ABIGAIL DESROSIERS, HDSA’s Massachusetts and Rhode Island Chapter President. “Every day I am blown away by the hard work and dedication of our organization to put these events together - it makes me proud to be involved. The spirits of our community will bring a beautiful event to Colt State Park and I look forward to seeing everyone there.”

Team Hope is HDSA’s largest national grassroots fundraising event, which takes place in over 100 cities across the U.S. and has raised more than $20 million for HD since its inception in 2007. Thousands of families, friends, co-workers, neighbors, and communities walk together each year to support HDSA’s mission to improve the lives of people affected by HD and their families.

For more information about the event, please contact Abigail Desrosiers (abigaildesrosiers18@gmail.com, 978-995-7798). Online registration and donation can be found at hdsa.org/thwrhodeisland

HDSA’s Team Hope Walk Program is nationally sponsored by Genentech and Teva Pharmaceuticals.

HCV healthcare leaders at July WaterFire

RI Defeats Hep C partnered with WaterFire on July 30th after a two-year hiatus due to the COVID-19 pandemic. Torchbearers included RI’s hepatitis C virus (HCV) medical, public health and advocacy leaders, who reunited and re-committed to HCV elimination. This year’s theme was “Test to Treat,” to get all Rhode Islanders with HCV diagnosed and promptly treated and cured. [PHOTO COURTESY OF LYNN TAYLOR, MD]
Recognition

HopeHealth, URI graduate first nursing fellows in palliative care

KINGSTON – University of Rhode Island nursing students BECCA ALLDER and KATIE FITZMAURICE graduated from a summer of clinical training and practice in one of healthcare’s fastest-growing fields, becoming the inaugural fellows of the Susan Flynn Palliative Care Nursing Fellowship.

The fellowship is a new partnership between HopeHealth, the University of Rhode Island College of Nursing and the Susan Flynn Oncology Nursing Development Program aimed at addressing the growing need for nurses with experience in palliative care.

Over eight weeks, Allder and Fitzmaurice shadowed HopeHealth’s palliative care experts and met with multidisciplinary teams. They also researched and reviewed clinical practice and literature supporting topics that are critical to patients and families receiving palliative care. As fellows in the program, they prepared and delivered evidence-based research presentations on the influence of comfort feeding on patient quality of life, and the impact of respite care for pediatric palliative patients.

“Palliative care is committed to providing person-centered care that is based on the seriously ill person’s and family’s beliefs, values, and goals,” says SUSAN DESANTO-MADEYA, PhD, APRN-CNS, FAAN, who holds the Miriam Weyker Endowed Chair for Palliative Care at the URI College of Nursing. “This fellowship is a powerful way to advance that commitment for future generations of nurses, thanks to hands-on experience with a leading team of experts.”

The Susan Flynn Palliative Care Nursing Fellowship is the most recent expansion of the Susan Flynn Oncology Nursing Development Program, founded by Fred Flynn in honor of the care that his late wife, Susan, received after a diagnosis of ovarian cancer. The program’s namesake oncology fellowship, created in 2014, has already produced 262 oncology nursing fellows from more than 10 hospitals.

Now, Allder and Fitzmaurice join their ranks as the program’s first two palliative nursing fellows.

“The more we can educate and inspire future nurses about palliative care, the better quality of life we give to a growing population of patients,” says HopeHealth President & CEO DIANA FRANCHITTO. “As a regional leader in palliative care, HopeHealth is uniquely positioned to do just that. It was a privilege to be part of the experience of our first two fellows and show them firsthand what a difference palliative care makes in the lives of patients and families living with serious illness.”

URI nursing students Becca Allder (left) and Katie Fitzmaurice (right) were celebrated as the inaugural graduates of the Susan D. Flynn Palliative Care Nursing Fellowship, a new partnership for HopeHealth and the URI College of Nursing.
Obituary

ANTHONY F. MERLINO, MD, 92, of North Providence, passed away August 9th, surrounded by his family. He was the beloved husband for 58 years to the late Dolores Mary [Aucello] Merlino.

Dr. Merlino was a graduate of Classical High School, Providence College, University of Connecticut, and Jefferson Medical College, and served as a Medical Officer in the USAF, 2 years on active duty, and several years in the Active Reserve.

He was a board-certified orthopedic surgeon, who practiced at the Fatima and Providence units of St. Joseph Hospital, until his retirement, after 40 years, in 2003. He authored over 20 scientific articles in various medical journals and was a member of the American Medical Association, American College of Surgeons, American Academy of Orthopedic Surgeons, Rhode Island Orthopedic Society, Eastern Orthopedic Association, Boston Orthopedic Club, and numerous other professional organizations. Historically, with his late partners, William Hindle, MD, and Ralph Pike, MD, he founded the first professional service corporation in Rhode Island, the Rhode Island Orthopedic Group, Inc. on January 2, 1969.

For a period of 20 years, he was orthopedic consultant to his beloved Alma Mater, Providence College and team physician to its NCAA Division I Athletic Teams. He was honored by the College with the McDonnell Award in 1981 and the Golden Friar Alumni Service Award in 2001.

Dr. Merlino was a daily communicant of St. Anthony Church in North Providence and a member of the Archangelica Prayer Cenacle. He was a major benefactor of his church, of Providence College and Jefferson Medical College, and a serious contributor to a multitude of other charitable organizations and foundations.

He was a serious JFK assassination researcher and devoted many years of his life to that activity. He was a skilled film and digital photographer, who specialized in landscapes and wildlife. He was also an accomplished pianist, who played for his own enjoyment and that of his family and friends.

He was the devoted father of Christa Merlino of Smithfield and Paula DeDonato and her husband Joseph, and the proud and loving grandfather of Christina and Joseph DeDonato, all of North Providence. He was the brother of Frank Merlino and his wife Elizabeth of Potowamut, and Helen Toro of West Warwick and Estero, FL.

Memorial donations may be made to the Anthony F. Merlino, MD, Scholarship Fund of Providence College, 549 River Avenue, Providence, RI 02918.