SPECIAL SECTION: PART I

UPDATES in INFLAMMATORY BOWEL DISEASES

GUEST EDITORS: ABBAS H. RUPAWALA, MD; JASON M. SHAPIRO, MD; SAMIR A. SHAH, MD
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Introduction: Updates in Inflammatory Bowel Diseases

Inflammatory Bowel Diseases (IBD), including Crohn’s disease (CD), ulcerative colitis (UC) and IBD unspecified (IBDU), are chronic immune-mediated diseases affecting the luminal gastrointestinal system. The incidence of IBD is rising worldwide, particularly in developing countries. In the United States (US) in 2015 an estimated 3 million adults (1.3% of the US adult population) lived with a diagnosis of IBD. This estimate did not include pediatric patients. Over the last 20 years, there have been significant advances in our understanding of the etiopathogenesis of IBD, discovery of newer agents for management of these diseases, and a paradigm shift in the approach to managing them. In this issue and the following issue of the Rhode Island Medical Journal, we present updates on a wide range of topics related to care of patients with IBD written by experts in adult and pediatric gastroenterology, colorectal surgery, and other fields from within the state. We are also fortunate to have contributions from national and international experts on many of these topics from across the country. Each topic covers clinically relevant information that should serve as a quick reference guide for busy clinicians in the inpatient and outpatient settings. Given the number of topics to be covered, we have split them over two consecutive issues. The editors include Dr. Samir A. Shah, who is a leading expert on IBD in Rhode Island, Chief of Gastroenterology at The Miriam Hospital, and Immediate Past President of the American College of Gastroenterology; Dr. Jason M. Shapiro, Director of the Pediatric IBD Center at Hasbro Children’s Hospital and Director of Research in the Division of Pediatric Gastroenterology, Nutrition and Liver Diseases; and Dr. Abbas H. Rupawala, previously Co-Director of the IBD Center at Brown Medicine and now Director of the IBD Center at the University of Massachusetts Medical Center.

Preventive Care and Health Maintenance in Patients with IBD

Patients with IBD will often need treatment with immunosuppressive medications that carry an increased risk of infections and malignancies. Therefore, health maintenance with specific focus on vaccination and cancer surveillance is of paramount importance, particularly as our patients live longer with these conditions and may remain on treatment for prolonged periods of time. These concepts have been succinctly covered in this topic by Dr. Daniela Fluxa and Dr. Breton Roussel, both trainees in gastroenterology, and Dr. Jana Alhashash. The senior author on this topic, Dr. Francis Farraye, is an internationally renowned expert on this topic and is also the lead author of the American College of Gastroenterology’s (ACG) clinical guidelines on preventive care in IBD.

Extrainestinal Manifestations of IBD

Patients with IBD are at increased risk of developing other autoimmune diseases. However, more commonly, they will exhibit symptoms related to other organ systems, typically involving the joints, skin and eyes. Many of these patients benefit from multidisciplinary care at the Rhode Island Hospital Center for Skin and Musculoskeletal Diseases. Some extraintestinal symptoms may parallel disease activity of IBD while others may manifest independently of the bowel inflammation activity. Furthermore, patients with IBD are at risk of several complications affecting every organ system. Dr. Sean Fine, Director of the IBD Center at Brown Medicine/Brown Physicians, Inc., has provided a comprehensive summary of the extraintestinal manifestations of IBD and their management.

Clostridioides Difficile and FMT in Patients with IBD

Over the last decade there has been an epidemic of Clostridioides difficile infection (CDI), in part due to the rampant use of antibiotics that has led to significant interest and education in antibiotic stewardship. It was also, in large part, due to the emergence of a hypervirulent strain of C. difficile characterized as North American pulsed-field type 1, restriction-endonuclease analysis group type BI, and PCR ribotype 027. Patients with IBD seem to have increased risk of CDI even in absence of antibiotic use, in part due to the dysbiotic gut microbiome, and are at higher risk of adverse outcomes. Furthermore, fecal microbial transplant has emerged as a promising treatment modality in multiply recurrent CDI. However, given the effect of microbiome perturbations on the course of IBD, FMT requires special consideration in this patient population, particularly as we explore FMT as an emerging therapeutic modality for this condition.

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Sohum Patwa, resident in internal medicine at Rhode Island Hospital (RIH), and Dr. Christopher Ward, former chief resident at RIH and currently a gastroenterology fellow at the Lahey Clinic, accompany Dr. Colleen Kelly, an associate professor of medicine at Brown, world-renowned expert in FMT and lead author of the recent ACG guidelines on management of CDI, discuss the features of CDI in IBD patients and the nuances of FMT in this population.

**TREAT-TO-TARGET: THE ERA OF BIOLOGICS IN IBD MANAGEMENT**

One of the major paradigm changes in the management of IBD over the last decade is the shift of goals of treatment from improvement in symptoms alone to healing gut inflammation. This concept is inspired from care of patients with rheumatoid arthritis, where the focus of treatment has evolved to healing joint inflammation with the goal of preventing long-term joint damage and preserving organ function. This concept is discussed at length in the manuscript written Dr. Daniel Marino and lead editor Dr. Samir A. Shah. We are also fortunate to have input from renowned faculty across United States, including Dr. Siddharth Singh of the University of California San Diego, Dr. Jason Hou of the Baylor College of Medicine, Dr. Corey Siegel of Dartmouth-Hitchcock Medical Center, and Dr. Gil Melmed of Cedars-Sinai Medical Center. They also review the efforts of IBD Qorus, a nationwide quality improvement initiative aimed at improving care of patients with IBD. IBD Qorus now includes over 50 sites across the US that work in a collaborative fashion to improve care of IBD patients in a variety of different areas; their most recent focus is improving adoption of a treat-to-target approach in the care of IBD patients.

**PART II**

In the upcoming issue, we will cover the following topics:

- Lessons from the Ocean State Crohn’s and Colitis Area Registry (OSCCAR)
- Surgical Advances in IBD
- Management of the Hospitalized Patient with Acute Colitis
- Reproductive Issues in Women with IBD
- Nutritional Therapy in Inflammatory Bowel Disease
- Pediatric IBD
- COVID-19 and IBD: Lessons from SECURE-IBD

**References**


**Guest Editors**

Abbas H. Rupawala, MD, Division of Gastroenterology, UMass Chan Medical School, Worcester, Massachusetts.

Jason M. Shapiro, MD, Division of Gastroenterology, Nutrition and Liver Diseases, Hasbro Children’s Hospital, Providence, Rhode Island.

Samir A. Shah, MD, Chief of Gastroenterology, The Miriam Hospital, Providence, Rhode Island; Gastroenterology Associates, Inc., 44 West River Street, Providence, Rhode Island.

**Correspondence**

Abbas H. Rupawala, MD
Abbas.rupawala@umassmed.edu
Preventive Care and Health Maintenance in Patients with Inflammatory Bowel Disease
DANIELA FLUXA, MD; BRETON ROUSSEL, MD; JANA G. HASHASH, MD, MSc; FRANCIS A. FARRAYE, MD, MSc

ABSTRACT
Health maintenance in patients with inflammatory bowel disease (IBD) is essential. In order to achieve clinical and endoscopic remission, many patients will require treatment with steroids, immunomodulators, biologics or small molecules, which place them at a higher risk of serious infections as well as certain malignancies. Some of these adverse events are preventable through vaccination and adherence to cancer screening guidelines, making preventive care and health maintenance in this patient population crucial. Gastroenterologists should take a proactive role in health care maintenance and collaborate with the patient’s primary care provider. The aim of this article is to review and provide guidance on preventive care and health maintenance in patients with IBD, including vaccinations, cancer screening, bone health, nutrition, and mental health assessment as well as smoking cessation.

KEYWORDS: health maintenance; inflammatory bowel disease (IBD); preventive medicine; screening

INTRODUCTION
Inflammatory bowel disease (IBD) consists of a spectrum of diseases including ulcerative colitis (UC), Crohn’s disease (CD) and indeterminate colitis. These are chronic inflammatory conditions of the bowel that may affect patients of any age range with a peak incidence during the second to fourth decade of life. It has been estimated that the number of people worldwide living with IBD had increased from 3.7 million to more than 6.8 million between 1990 and 2017, with nearly a quarter of these patients living in the United States. IBD is a complex condition and many patients with IBD will require immunosuppressing therapies with corticosteroids, immunomodulators, small molecules and/or biologic agents. For this reason, many patients with IBD are at an increased risk of infections, malignancy and other complications. Up-to-date health maintenance is paramount in patients with IBD as a means of limiting morbidity from the disease itself and its treatment. Data suggests that patients with IBD do not receive adequate preventive care as compared to the general population, and even though health maintenance guidelines from different GI societies are available, adherence to preventive care recommendations, especially vaccination, remain low. Moreover, many patients with IBD consider their gastroenterologist as their primary care provider (PCP). For these reasons, it is imperative that gastroenterologists take a proactive role in health maintenance in these patients. It is of equal importance to partner with PCPs in optimizing health maintenance. The intent of this article is to review and provide guidance on preventive care and health maintenance in patients with IBD, including vaccinations, cancer screening, bone health, nutrition, and mental health assessment as well as smoking cessation.

VACCINES
Patients with IBD are susceptible to acquiring infections for two reasons: immunological disorder caused by the disease itself, as well as treatment side effects. Over the last two decades, the advent of new biologic agents and small molecules revolutionized the treatment of IBD. These medications are proven to be beneficial in controlling disease activity but may also place the patient at a higher risk for serious and/or opportunistic infections, a number of which are vaccine preventable. In general, patients with IBD are recommended to follow standard, age-appropriate immunization schedules, with immunizations occurring ideally prior to initiation of immunosuppressive therapy, as some of these therapies may blunt vaccine response. Special consideration must be kept for live-attenuated vaccines, which are contraindicated in immunosuppressed patients, particularly those who are moderately-severely immunosuppressed. Patients with IBD are considered to be moderately-severely immunosuppressed if taking any of the following medications: systemic steroids with doses of ≥20 mg for ≥2 weeks, methotrexate [MTX] >20 mg per week or >0.4 mg/kg/week, azathioprine [AZA] ≥3 mg/kg/day, 6-mercaptopurine (6-MP) ≥1.5 mg/kg/day, cyclosporine, biologic agents (except for vedolizumab) and small molecules. Of note, significant protein calorie malnutrition is also linked with immunosuppression. Low dose immunosuppression includes receiving treatment with topical steroids [oral budesonide >6 mg/day] and those on lower doses of systemic steroids, MTX, AZA and 6-MP. In contrast to patients who are moderately-severely immunosuppressed, certain live vaccines may be safe...
during low-dose immunosuppression or in patients on certain biologic agents; however, the decision to administer any live vaccine should be considered on a case-by-case basis.\cite{7,8} Examples of commonly used live-attenuated vaccines include measles-mumps-rubella (MMR) vaccine, varicella (VAR) vaccine, nasal influenza and the live herpes zoster vaccine (no longer available in the United States). Other live vaccines include yellow fever, cholera and one of the existing typhoid vaccines which are usually administered for travel purposes.\cite{2} Otherwise, all adult patients with IBD may receive non-live vaccines including inactivated influenza vaccine, pneumococcal vaccines, hepatitis A and B vaccine, tetanus-diphera and pertussis (Tdap), human papilloma virus (HPV) vaccine, meningococcal vaccine, inactivated recombinant herpox zoster vaccine and adenovirus, subunit or messenger RNA (mRNA) vaccines directed against coronavirus virus disease (COVID-19).\cite{2} Current vaccination recommendations in adult patients with IBD are summarized in Table 1, see Appendix. Given COVID-19 vaccinations are dynamically changing as the pandemic evolves, would recommend visiting the Center for Disease Control and Prevention websites for updated information. Pediatric recommendations on regards to COVID-19 vaccination are also available in these websites: [https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html and https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html].

Regarding optimal timing for vaccination, the Infectious Diseases Society of America (IDSA) guidelines recommend that the administration of live vaccines should occur at least 4 weeks prior to initiating immunosuppression and should be avoided within 2 weeks of initiation of immunosuppression.\cite{9} On the other hand, if a live vaccine is required and the patient has discontinued immunosuppressive therapy, it is recommended to at least wait for 1–6 months (five times the elimination half-life of a drug) prior to the live vaccine administration,\cite{7} or if there is no detectable drug in the system for medications in which there are options to measure. For inactivated vaccines, the IDSA recommends administration at least 2 weeks prior to initiating immunosuppression.\cite{9}

Employing a “cocoon strategy”, vaccinating household and close contacts is also an important approach. Healthy immunocompetent individuals who live in a household with immunocompromised patients should receive inactivated vaccines as per their age-appropriate schedules, and the following live vaccines based on the Centers for Disease Control and Prevention (CDC) annual schedule: MMR vaccine, rotavirus vaccine in infants 2–7 months (immunocompromised patients should avoid handling diapers of vaccinated infants for 4 weeks following vaccination), VAR vaccine, and in cases when the inactive zoster vaccine is not available, the live zoster vaccine is recommended. Immunocompromised patients should avoid individuals who develop skin lesions after receiving the VAR or the live zoster vaccines until the lesion disappear.\cite{9} Household and close contacts may also receive the following live vaccines for travel: yellow fever and oral typhoid vaccine, while the oral polio vaccine should not be administered under any circumstances.\cite{9}

**CANCER SCREENING**

**Colon Cancer**

Colonoscopy remains the primary modality used for colorectal cancer and dysplasia surveillance in patients with IBD. Two-step modalities such as fecal immunochemical test (FIT) or multi-targeted stool DNA tests (like Cologuard™) are not appropriate for CRC surveillance in the IBD population.\cite{10} The interval of screening and/or surveillance differs based on the duration and extent of disease. Dysplasia surveillance using high-definition colonoscopy should begin 8 years after disease diagnosis in patients with UC with involvement extending proximal to the rectum, or in patients with CD who have more than 1/3 of the colon involved.\cite{11,12,13} Subsequent surveillance colonoscopies should be completed every 1-5 years following a negative colonoscopy based on additional patient risk factors for developing dysplasia or clinical features that could potentially obscure the detection of dysplasia (Table 2).\cite{12} A personal history of dysplasia, adenomatous polyps, primary sclerosing cholangitis, family history of CRC, degree and extent of colonic inflammation, extensive pseudopolyps all inform increased frequency of surveillance. Patients with primary sclerosing cholangitis (PSC) should undergo a colonoscopy at time of

**Table 2. Interval of time to next colonoscopy following a colonoscopy negative for dysplasia**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Interval after Negative Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>Ongoing moderate or severe inflammation, PSC, Family history of CRC in first degree relative diagnosed age ≤50 years, Extensive pseudopolyps, History of invisible dysplasia or high-risk visible dysplasia* in last 5 years</td>
</tr>
<tr>
<td>2–3 years</td>
<td>Mild inflammation, Family history of CRC but no first degree relative ≤50 years, Endoscopic evidence of prior severe colitis such as scarring or moderate polyposis, History of invisible dysplasia or high-risk visible dysplasia* diagnosed &gt;5 years prior</td>
</tr>
<tr>
<td>5 years</td>
<td>Continuous disease remission with mucosal healing on colonoscopy and one of the following: No dysplasia on ≥2 consecutive colonoscopies, Minimal historic colonic involvement i.e. &lt;1/3 of the total colon</td>
</tr>
</tbody>
</table>

*High risk visible dysplasia: >2cm, lateral spreading, irregular boarder, local recurrence, incomplete prior resection.

Table published in the 2021 AGA Clinical Practice Update on Endoscopic Surveillance of Colonic Dysplasia (12).
diagnosis and then annually. Chromoendoscopy during surveillance can be used at the discretion and expertise of the endoscopist with the potential of increasing detection of subtle lesions.

**Cervical Cancer**
Women with IBD on immunosuppressants are at an increased risk of developing cervical cancer or high-grade dysplasia. For this reason, the American College of Obstetrics and Gynecology and American College of Gastroenterology (ACG) recommend an increased frequency of cervical cancer screening with annual cytology. Furthermore, the increased risk of cervical dysplasia and malignancy emphasizes the importance of vaccination for HPV when indicated.

**Skin Cancer**
Both melanoma, and non-melanoma skin cancers (NMSC) are observed more frequently in patients with IBD. Immunosuppression with either immunomodulators or biologics confer additional risk. For patients taking chronic thiopurines for longer than 1 year, the risk of developing NMSC was at least four times that of matched healthy controls. This association applies to both current and prior exposure to thiopurines. Similarly, there is a higher risk of being diagnosed with melanoma (OR 1.88, 95% CI 1.08-3.29) in patients with a history of IBD, and particularly in patients treated with biologic therapy. Primary prevention through behavioral modification such as sun avoidance and sunscreen use should be discussed with all patients with IBD. Furthermore, all patients with IBD should be referred for skin exam with a dermatologist. Given the durability of risk despite cessation of immunomodulators, annual skin exams should be continued lifelong in select patients as directed by dermatology.

**Bone Health/Osteopenia/Osteoporosis**
Patients with IBD are at increased risk of osteopenia, osteoporosis, and bone fractures due to multiple factors, including type of IBD, history of corticosteroid use, low body mass index, malnutrition, vitamin D deficiency, calcium malabsorption, underlying chronic inflammatory state, and immobilization. Published literature indicates that the risk of osteoporosis is estimated to be 15–40%. Recommendations on screening of osteopenia/osteoporosis and prevention in patients with IBD are detailed in Table 3.

**Nutritional Assessment**
Iron deficiency anemia is observed in approximately 45% of patient with IBD and occurs through multiple mechanisms, including luminal blood loss and decreased iron absorption. The presence of inflammation may confound the interpretation of iron studies, and a ferritin cut-off of 100 ng/mL should be considered as the lower limit of normal in patients with active IBD. A consequence of impaired absorption, oral iron repletion may be ineffective and parenteral infusions are often necessary. Similarly, vitamin B12 deficiency is well described in patients with ileal CD or those with a history of prior ileal resection. Cornerstones Health recommends screening for iron deficiency in all patients with IBD and vitamin B12 deficiency in patients with ileal CD or history of ileal resection. In patients at risk of B12 deficiency, methymalonic acid (MMA) levels should be checked simultaneously and B12 replacement therapy considered in all patients with elevated MMA level for a goal B12 level of greater than 400 pg/mL and normalization of MMA. Parenteral replacement should be considered in patients with greater than 20 cm of terminal ileal resection.

**Mental Health – Depression and Anxiety Screening**
Depression and anxiety are common disorders in patients with IBD with pooled mean rates almost twice as high when compared to healthy controls. While anxiety has been associated with decreased compliance to medications, increased risk of surgery and lower quality of life, depression has been linked with pain, IBD flare and lesser response to IBD treatment in some studies. Furthermore, depression severity has been associated with suicidal ideation in this patient population. Therefore, screening of these conditions is critical as they may cause significant morbidity. The Crohn’s & Colitis Foundation health maintenance checklist...
Smoke use is associated with an increased risk for the development of CD and for disease-specific complications such as progression, need for surgery, and surgical complications. Although there are data demonstrating decreased disease activity in patients with UC, tobacco should not be recommended because the overwhelming detriments of smoking on extra-intestinal health outweigh any benefits.

Despite clear evidence for the negative effects of smoking, up to 20% of patients with CD and 60% of patients with UC reported believing that smoking was either neutral or beneficial for their disease activity. Furthermore, 21% of patients with CD and 44% of patients with UC within the same cohort were never asked about their smoking status. Society guidelines emphasize the need to screen for tobacco use at every encounter.

TOBACCO USE/SMOKING CESSATION

Healthcare maintenance remains a crucial issue in the care of patients with IBD. Despite their importance, many physicians do not address these factors due to lack of knowledge, time constraints, or because they do not feel that this is their responsibility. Checklists are now available to help gastroenterologists and PCPs ensure that their patients with IBD are receiving appropriate vaccinations and other screenings.

References


Extraintestinal Manifestations of Inflammatory Bowel Disease

SEAN FINE, MD, MS

ABSTRACT

Inflammatory bowel disease (IBD) is primarily a disease of the digestive tract system, though it may affect other organ systems outside of the intestines. Extraintestinal manifestations (EIMs) can occur in up to one third of patients with Crohn's disease or ulcerative colitis. The most common EIMs involve dermatologic and musculoskeletal manifestations. EIMs may either parallel intestinal inflammation or be completely independent of disease activity. Physicians should be aware of EIMs and think systematically when evaluating patients with IBD, as nearly every organ can be involved, and a multidisciplinary treatment approach should be undertaken to improve outcomes and quality of life.

KEYWORDS: inflammatory bowel disease; extra intestinal manifestations; Crohn's disease; ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD), Crohn’s disease (CD), and ulcerative colitis (UC) are chronic immune-mediated diseases of the gastrointestinal tract. The chronic inflammation is a result of a dysregulated immune response that leads to tissue inflammation and destruction. However, IBD should not solely be regarded as an intestinal disorder, but rather a systemic disease given that a significant number of patients will develop extraintestinal manifestations (EIMs). Between 25-40% of patients with IBD will develop EIMs and the presence of one confers the risk to develop subsequent EIMs. Rarely, up to five organ systems have been reported to be impacted at one time. Most patients who develop EIMs will do so after a diagnosis of IBD has been established. However, about 25% of patients will be diagnosed with an EIM initially, prior to uncovering a diagnosis of IBD. In a large IBD cohort study, the most common EIMs diagnosed prior to the onset of IBD included peripheral arthritis or axial arthritis, uveitis, and primary sclerosing cholangitis (PSC). Risk factors that have been strongly correlated with the development of EIMs include cigarette smoking, colonic disease, and perianal CD. Extraintestinal symptoms may involve virtually any organ system with a potential for a profound impact on the patient’s quality of life, in some instances more so than bowel disease. The most affected systems are the skin, musculoskeletal, and eyes, but several other organs may also be affected, including the kidneys, blood, and hepatobiliary.

The pathogenesis of EIMs in IBD is not clearly elucidated. The European Crohn’s and Colitis Foundation working group has defined the mechanism for EIMs to better standardize for scientific discovery and research as the following: “An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD.” Genetics, environmental triggers, and the intestinal microbiota have been postulated as potential culprits for the development of EIMs. Studies have demonstrated overlaps between genetic risk loci for IBD and EIMs and found a concordance for EIMs in parent-offspring pairs and sibling-pairs of 70% and 84% respectively. The most well-known genetic risk factor for central arthritis (Ankylosing spondylitis) in association with IBD is HLA-B27 positivity. Tobacco use has been shown to be associated with a higher risk for development of both skin and joint EIMs. The role of the intestinal microbiota in the pathogenesis of IBD is well established as an undesired and overacted immune response is directed at the intestinal flora. One of the hypothesized processes in which the microbiota plays a role in the development of EIMs is in part through molecular mimicry. Cross-reactivity of the immune system against other extra-intestinal sites occurs due to gut microbiota antigens sharing similar epitopes present on cells in organs. Another potential etiology of inflammation developing beyond the intestine may be attributed to loss of the intestinal barrier integrity, which then allows for bacterial flora and its components to translocate to distant sites and lead to an inflammatory response. The importance of the colonic microbiota in inflammation is seen in the findings that patients with IBD that involves inflammation of the colon develop EIMs at a higher rate compared to those with isolated small bowel disease.

It is important to differentiate EIMs from extraintestinal complications. EIMs are immune-mediated conditions which echo the immunologic mechanisms of inflammation in bowel disease, whereas extraintestinal complications (Table 1, see Appendix) arise from secondary processes that are direct
or indirect sequela of bowel damage (anemia, nephrolithiasis, Vitamin B12 deficiency) or related to medications used to manage the disease. EIMs can manifest in parallel with IBD disease activity or be completely independent (Table 2), sometimes being even more difficult to manage and treat than the bowel disease itself. Patient awareness through education and a multidisciplinary team approach are important key factors for early identification and treatment of EIMs that can lead to symptom resolution and improving quality of life.

### MUSCULOSKELETAL

Musculoskeletal symptoms represent the most common EIMs in IBD and are termed “seronegative spondyloarthropathies.” Peripheral small and large joints as well as axial joints may be affected in up to 40% of patients with IBD. Musculoskeletal EIMs can precede, occur concurrently, or develop following the diagnosis of IBD, often by as many as 10 years. Males and females are equally affected, but patients with colonic disease are more impacted than those with isolated small-bowel disease.

Peripheral arthritis is a migratory arthritis that shows little to no joint deformity, but inflammation may last up to several weeks. Peripheral arthropathy is divided into two types: type 1 and type 2. Type 1 is pauciarticular (typically involving fewer than 5 joints), seronegative, asymmetric and will often parallel disease activity. Joints that may be affected include the knees (most common), shoulders, hips, wrist, ankles, and elbows. Type 2 is polyarticular (involving 5 or more joints), symmetric, is independent of bowel disease, and typically affects the metacarpophalangeal joint. Type 2 is associated with an increased risk of uveitis. The diagnosis of type 1 and type 2 is based on clinical suspicion, as imaging is unrevealing due to the lack of joint destruction. Treatment for type 1 is based on addressing bowel disease whereas type 2 is more directed at symptoms with rest, intra-articular steroid injections, physiotherapy, or sulfasalazine. The selective COX-2 inhibitor, celecoxib, has been demonstrated to be a potential treatment option and used with caution in patients with IBD since it is not been found to be associated with inducing flares.

### Table 2. Extra-Intestinal Manifestations and Association with Bowel Disease Activity

<table>
<thead>
<tr>
<th>EIM</th>
<th>Parallels with Bowel Disease Activity</th>
<th>Unclear Association with Disease Activity</th>
<th>Independent of Bowel Disease Activity</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td>Treatment of intestinal inflammation</td>
</tr>
<tr>
<td>• Apathous Stomatitis</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pyostomatitis Vegetans</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
<td></td>
<td>Refer to Table 3</td>
</tr>
<tr>
<td>• Episcleritis</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Scleritis</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Uveitis</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Type 1 (&lt;5 joints)</td>
<td>✓</td>
<td></td>
<td></td>
<td>Treatment of intestinal inflammation</td>
</tr>
<tr>
<td>• Type 2 (≥5 joints)</td>
<td></td>
<td></td>
<td>✓</td>
<td>COX-2 inhibitors</td>
</tr>
<tr>
<td>Axial Arthritis</td>
<td></td>
<td></td>
<td></td>
<td>Sulfasalazine (notably in UC)</td>
</tr>
<tr>
<td>• Ankylosing Spondylitis</td>
<td></td>
<td></td>
<td></td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>• Sacroiliitis</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
<td></td>
<td>Treatment of intestinal inflammation</td>
</tr>
<tr>
<td>• Erythema Nodosum</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pyoderma Gangrenosum</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Sweet’s Syndrome</td>
<td></td>
<td></td>
<td></td>
<td>Treatment of intestinal inflammation</td>
</tr>
<tr>
<td>• Bowel associated dermatosis and arthritis syndrome (BADAS)</td>
<td>✓</td>
<td></td>
<td></td>
<td>Short course of systemic steroids if needed</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td></td>
<td>✓</td>
<td>Close monitoring and surveillance given strong malignancy association (cholangiocarcinoma, HCC, colon cancer, gallbladder cancer) Liver Transplantation for cirrhosis</td>
</tr>
</tbody>
</table>

Peripheral arthritis is a migratory arthritis that shows little to no joint deformity, but inflammation may last up to several weeks. Peripheral arthropathy is divided into two types: type 1 and type 2. Type 1 is pauciarticular (typically involving fewer than 5 joints), seronegative, asymmetric and will often parallel disease activity. Joints that may be affected include the knees (most common), shoulders, hips, wrist, ankles, and elbows. Type 2 is polyarticular (involving 5 or more joints), symmetric, is independent of bowel disease, and typically affects the metacarpophalangeal joint. Type 2 is associated with an increased risk of uveitis. The diagnosis of type 1 and type 2 is based on clinical suspicion, as imaging is unrevealing due to the lack of joint destruction. Treatment for type 1 is based on addressing bowel disease whereas type 2 is more directed at symptoms with rest, intra-articular steroid injections, physiotherapy, or sulfasalazine. The selective COX-2 inhibitor, celecoxib, has been demonstrated to be a potential treatment option and used with caution in patients with IBD since it is not been found to be associated with inducing flares.
Axial arthropathies occur less frequently than peripheral arthritis and includes both ankylosing spondylitis and sacroiliitis. These inflammatory joint processes affect males more than females and do not parallel bowel inflammation. Ankylosing spondylitis classically presents with a stooped posture and worsening back pain/stiffness in the morning or at night and is improved with physical activity. Physical exam may reveal limited spinal flexion and X-ray imaging of the lumbar spine will show a “bamboo spine” that represents complete fusion of the bones (Figure 1A). Nearly all patients with IBD who have the genetic mutation in HLA-B27 will develop ankylosing spondylitis. IBD-associated sacroiliitis (Figure 1B) is most often bilateral in nature and can be either symptomatic or asymptomatic. Asymptomatic sacroiliitis can be seen in up to 50% of patients with CD. Spinal and axial disease are treated similarly to other spondyloarthropathies. Patients should be given a formal exercise plan and work closely with physical therapy to prevent deformities. Therapeutic agents that may also be used in axial arthritis include sulfasalazine, immunomodulators (methotrexate and azathioprine), and anti-tumor necrosis factor (TNF) therapy.

DERMATOLOGIC

Cutaneous EIMs may occur in up to 15% of patients with IBD and require dermatologic evaluation to confirm and assist in management. The two most common skin findings in IBD are erythema nodosum (EN) and pyoderma gangrenosum (PG). EN often appears on the extensor surfaces of the lower extremities, commonly the anterior tibial area, and is characterized by red raised tender nodules about 1–5 cm in diameter (Figure 2A). Although lesions may not be easily visible, physical exam will reveal tender palpable areas. Diagnosis is based on clinical judgement and skin biopsies are not necessary to make a diagnosis but would reveal inflammation of subcutaneous fat (panniculitis). EN shows a preponderance in females to males, associated with eye and joint involvement, and has a higher prevalence in CD than UC. The development of lesions parallels disease activity and thus treatment is aimed at addressing the ongoing bowel inflammation. Importantly, EN has been shown in a retrospective study to carry a 6-fold risk of development IBD within 3 years of presentation so this physical exam finding should prompt clinicians to always have a high index of suspicion for IBD. EN has been shown in a retrospective study to carry a 6-fold risk of development IBD within 3 years of presentation so this physical exam finding should prompt clinicians to always have a high index of suspicion for IBD. 

PG can be a debilitating skin disorder that occurs in about 5% of patients with IBD and is characterized by a discrete ulcer with a necrotic base, irregular violaceous edges, and purulent material which is sterile on culture. PG usually occurs on the lower extremities (Figure 2B) but may occur anywhere on the body notably, adjacent to a postsurgical stoma on the abdominal wall. These ulcers can range in size from a few centimeters to an entire limb. PG exhibits pathergy, a significant physiologic response to minor trauma or injury. Therefore, biopsy of the lesion should be avoided and the diagnosis is made clinically. It affects women more than men and it is unclear if PG has an association with clinical intestinal disease activity but in some instances may resolve with treatment of IBD. Mild cases may be treated with topical or local therapy that consists of steroid injections and moist dressings, but often...
systemic agents are needed that include dapsone, corticosteroids, and anti-tumor necrosis factor (TNF) therapy as well as involvement of a vascular surgeon specialist.

Acute febrile neutrophilic dermatosis, Sweet’s syndrome, is a rare EIM characterized by sudden onset tender erythematous papules and plaques on the upper extremities, trunk and face in association with fever and leukocytosis. Most cases occur in females, parallel intestinal disease activity, and are associated with other EIMs like arthritis. Treatment recommendations include topical or systemic steroids as well as adequate treatment of the IBD. Bowel associated dermatosis-arthritis syndrome (BADAS) is another rare neutrophilic dermatosis manifestation that was initially described in patients who had undergone ileojejunal bowel surgery but can also occur in patients with IBD. It presents with constitutional symptoms that include fever, arthritis, and arthralgias that precede an inflammatory skin eruption. Skin findings are characterized by erythematous macules that evolve into purpuric papules and vesiculopustular lesions on the upper extremities and trunk (Figure 2C). The pathophysiology is thought to involve immune complex creation in response to antigens from intestinal bacterial overgrowth that then deposit in the skin and synovium.17,18 Therapy for BADAS syndrome should focus on addressing the underlying intestinal inflammation in patients with IBD.

ORAL AND OCULAR

Oral lesions are common in patients with IBD but are found more often in patients with CD rather than UC, more prevalent in children compared to adults, and are found more commonly in men than women.19 The classic oral lesion associated with IBD is aphthous stomatitis, commonly referred to as a “canker sore”, presents as a shallow painful ulceration with a central fibrinous exudate and an erythematous border and can lead to symptoms of dysphagia or odynophagia. The lesions are commonly located along the buccal and labial folds but may also be present on the tongue (Figure 3A) or in the oropharynx. In a small number of patients, this may be the initial clinical exam finding on presentation, but most often are diagnosed after intestinal involvement has occurred.20 Aphthous stomatitis is common in the general population as well as other immune mediated diseases, but this finding is reported in up to 25% patients CD and 10% with UC.21 The presence of aphthous stomatitis becomes more severe with active bowel disease. Treatment mainly consists of topical steroids and anesthetics as well as addressing bowel disease with anti-inflammatory medications.

Pyostomatitis vegetans (PV) is a much less common occurrence but is an important oral manifestation of IBD for providers to be aware of. PV is commonly associated with UC but may also present in patients with CD. Intestinal manifestations will often predate PV development and patients will present with numerous tender miliary sterile pustular eruptions anywhere on the oral mucosa in a linear arrangement that may resemble “snail tracks.” Similarly, treatment of this presentation is achieved by addressing the bowel inflammation as well as topical steroids and antiseptic mouthwashes.

Ocular manifestations in IBD occur in 0.3–5% of patients and often associated with concomitant musculoskeletal manifestations. The ocular findings in patients with IBD that practitioners may encounter include episcleritis, scleritis, and uveitis. Being able to differentiate amongst these is of vital importance to early identify, appropriately treat, and prevent long-term patient morbidity (Table 3). Episcleritis is defined by hyperemia of the episcleral, which is the vascular plexus and fibrous tissue layer between the conjunctiva and sclera. It is a relatively benign manifestation and has no effect on vision. Eye exam reveals sectoral or diffuse patches of redness secondary to the inflamed superficial episcleral vessels (Figure 3B). Episcleritis often parallels bowel disease activity. Scleritis is a more pressing inflammation that affects the deeper layers of the eye, “the white of the eye”, and if not identified early can lead to visual impairment. Patients often have significant pain, classically deep boring pain that awakens the patient from sleep.22 One key exam feature to differentiate episcleritis from scleritis is the deep episcleral vascular plexus does not blanch when topical phenylephrine
In inflammatory bowel diseases (IBD), updates include the following:

**Scleritis**
- Redness, eye pain with associated tenderness to palpation, deep boring pain that awakens patient from sleep.
- Urgent diagnosis.
- No blanching of blood vessels when phenylephrine drops applied.
- Violaceous hue.
- Systemic steroids or immunosuppression may be required.

**Episcleritis**
- Redness, burning, itching (Never any vision changes, photophobia, or change in pupillary response to light).
- Non-Urgent diagnosis.
- Blood vessels blanch when phenylephrine drops applied.
- Treat underlying IBD.
- Cool compress and/or topical steroids.

**Uveitis**
- Redness, eye pain, blurred vision, photophobia.
- Urgent diagnosis.
- Requires slit lamp exam.
- Topical and systemic steroids.
- Severe/refractory cases may require systemic immunosuppression.

**Hepatopancreatobiliary**
Up to 50% of patients with IBD may experience hepatopancreatobiliary manifestations and complications during their disease course that may include gallstones, portal vein thrombosis, autoimmune hepatitis, autoimmune pancreatitis (Type 2), and primary sclerosing cholangitis (PSC). PSC is a chronic cholestatic liver disease that is characterized by fibrosis of the intrahepatic and extrahepatic bile ducts. Workup for PSC should be pursued in patients with IBD in the setting of elevated alkaline phosphatase or gamma-glutamyl transferase serum levels. Radiographic images will demonstrate multifocal bile duct strictures and segmental dilation, classically described as “beads on a string.” PSC is strongly linked to UC where at least 75% of patients with PSC have coexisting UC. Overall, a small number of patients with IBD will have PSC, 5% of UC patients and 2% of patients with CD (mainly colonic). Risk factors for the development of PSC in patients with UC are pancolitis, history of appendectomy, and male gender. There is a strong association (10-fold risk) for the development of colorectal dysplasia/and or cancer in patients with PSC and therefore patients should undergo initial colonoscopy at the time of diagnosis and then yearly thereafter. Gallbladder polyps in association with PSC have a high malignant potential and therefore screening by yearly ultrasound and if found should undergo treatment with cholecystectomy. Other potential complications that may arise from PSC include the development of acute bouts of acute cholangitis, cholangiocarcinoma, progression to liver fibrosis/cirrhosis, and acute decompensation requiring liver transplant. There are currently no recommended treatments for PSC and addressing the underlying bowel inflammation does not affect progression of PSC; however, management of patients requires a multidisciplinary team approach.

**Renal**
Nephrolithiasis is prevalent at a higher rate in patients with IBD compared to the general population and represents an extraintestinal complication of IBD. Renal stone formation can ultimately lead to repeated episodes of abdominal pain, chronic interstitial nephritis and, consequently, chronic kidney disease. One particular type of stone formation is closely associated with CD and an intact colon. Calcium-oxalate stones form due to depletion of bile acid salts secondary to inflamed or resected ileum. Bile acid salts are required for fat absorption; however, when inadequate amounts are present, fat can no longer be absorbed. This leads to calcium preferentially binding to fat rather than oxalate. Oxalate is then able to be easily reabsorbed by the colon and ends up in the urinary tract, leading to stone formation.

**Hematologic**
Patients with IBD are at an increased risk for venous thromboembolism (VTE) such as deep vein thrombosis, portal vein thrombosis, and pulmonary embolus. The etiology is multifactorial in nature stemming from active inflammation, nutritional deficiencies, and hospitalizations/surgeries that lead to immobility. The risk for VTE in patients with IBD is 3-fold higher than the general population. Several IBD-phenotype risk factors have been reported to be independent risk factors for VTE that include fistulizing disease, colonic involvement in CD, and extensive disease in patients with
The highest risk factor for VTE is in patients who are hospitalized with acute severe colitis.\textsuperscript{28} Prevention of VTE is critical in IBD patients who are hospitalized and providers should order the appropriate prophylactic medications even in most settings of patient-reported gastrointestinal bleeding in order to prevent this complication.

**CONCLUSION**

EIMs are common in both CD and UC and may have profound impacts on patients. While some EIMs may parallel bowel disease activity, others have an independent disease course that requires lifelong management and monitoring. It is important for providers in all specialties to have an awareness of the prevalence and clinical presentations of EIMs to best identify and implement therapeutic treatments to improve the quality of life for patients with IBD.

**References**

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Author
Sean Fine, MD, MS, Department of Medicine, Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, Rhode Island.

Correspondence
Sean Fine MD, MS
Director, Center for Inflammatory Bowel Disease
Brown Medicine
375 Wampanoag Trail
Riverside RI, 02915
401-649-4030
Fax 401-649-4031
sean_fine@brown.edu
FMT: What’s Next?
A Narrative Review of Fecal Microbiota Transplantation in Clostridioides difficile Infection and Inflammatory Bowel Disease

SOHUM A. PATWA, MD; CHRISTOPHER WARD, MD; COLLEEN R. KELLY, MD, FACG

ABSTRACT
Fecal microbiota transplantation (FMT) is an increasingly employed treatment option for Clostridioides difficile infection (CDI), with growing data supporting its safety and effectiveness in patients with concurrent inflammatory bowel disease (IBD). Given that alterations in the gut microbiome are associated with both ulcerative colitis (UC) and Crohn’s disease (CD), the use of FMT for the treatment of IBD itself is another area of active investigation. In this narrative review, we highlight the evidence for use of FMT in the treatment of CDI in patients with IBD, as well as for IBD alone, and provide insight into the future of microbiome therapeutics.

KEYWORDS: fecal microbiota transplantation; Clostridioides difficile infection; inflammatory bowel disease

INTRODUCTION
The normal gastrointestinal microbiome contains a delicate and diverse balance of bacteria and other microorganisms which are increasingly recognized to play a major role in health and disease. Fecal microbiota transplantation (FMT) is a powerful therapeutic option in conditions caused by an imbalance in the microbiota, or dysbiosis, such as Clostridioides difficile infection (CDI). FMT aims to restore gut homeostasis through the reintroduction of the community of organisms contained in the fecal material of healthy donors.

The use of FMT in Western medicine was first described in 1958 for the treatment of pseudomembranous enterocolitis.1 It remained rarely utilized until the early 2000s, when the rates of multiply recurrent CDI, refractory to standard antibiotic therapies, sharply increased.2 After a number of cohort studies and randomized-controlled trials (RCTs) demonstrating high efficacy,3-7 FMT is now considered a standard treatment option for CDI. The American College of Gastroenterology (ACG) 2021 guidelines on the treatment of CDI recommended the consideration of FMT for patients after a second or further episode of recurrent CDI and for patients with acute, severe and/or fulminant CDI that is refractory to antibiotic therapy, especially when patients are poor surgical candidates.8

In addition to being effective for the treatment of CDI in patients with IBD, FMT may also be effective in the treatment of IBD itself, as several RCTs have shown promising results.8,12 However, FMT for this indication is still considered investigational and only permissible within clinical trials being performed under an investigational new drug application (IND).13

The process of FMT includes donor selection, serological and stool screening for transmissible infections, anaerobic or aerobic preparation and processing of fecal material, and homogenization of stool to a form which can be administered to the recipient (Figure 1).11,14 Delivery of FMT through colonoscopy or capsules appears to be most effective15,16 though enema delivery may be considered in some circumstances.8

In this narrative review, we discuss the evidence surrounding use of FMT in the treatment of CDI in patients with IBD, as well as for IBD alone. Additionally, we provide insight into future investigations around microbiota therapeutics for these indications.

Figure 1. Preparation of donor stool in saline.
Fecal Microbiota Transplantation for Clostridioides Difficile Infection in Patients with Inflammatory Bowel Disease

In patients with IBD, many variables can predispose to C. difficile colonization and infection, including increased exposure to antimicrobials, immunosuppression, and altered [reduced, less diverse] fecal microbiota. Patients with IBD tend to suffer from more severe CDI owing to an increased prevalence of virulent and refractory C. difficile strains in this population. Patients with IBD who contract CDI are at increased risk of IBD flare, hospitalization, C. difficile carriage, recurrence, and death.

The most recent evidence on the use of FMT in patients with IBD is gathered in a meta-analysis from Tariq et al, who reviewed 25 observational studies addressing the use of FMT for recurrent C. difficile infections in both the adult and pediatric IBD populations. Of the 25 studies included in this meta-analysis, one was a prospective study, the remainder were retrospective. In their analysis, single (i.e., one-dose) FMT was associated with a pooled CDI cure rate of 78% in both the adult and pediatric populations. The definition of cure rate varied by study, ranging from clinical resolution to clinical remission to endoscopic resolution. In studies reporting single and multiple FMTs combined, the pooled cure rate was 88% in the adult population and 77% in the pediatric population, a difference that was significant in the adult population.

Based on early case reports, there was concern that altering the microbiome of the recipient through FMT could lead to worsened IBD symptoms or negatively impact the trajectory of the underlying disease process. In their meta-analysis, Tariq et al found that after FMT, a pooled 26.8% of adult patients experienced an IBD flare, which was defined in most studies as escalation of therapy and/or worsening symptoms. Conversely, the authors of seven studies in this meta-analysis noted that a pooled 33.8% patients had an improvement in IBD symptoms after FMT. This improvement may reflect the notion that FMT may treat underlying IBD symptoms – a concept addressed in later sections of this review.

A systematic review analyzing side effects of FMT for the treatment of CDI [without underlying IBD] found that amongst 1089 patients, most common adverse events included abdominal discomfort, fever, and nausea. Serious adverse events (SAEs) included severe infection (2.5%) and death (3.5%), though the authors of this review acknowledged that many of the studies suffered from small sample sizes. Tariq et al noted that the most common adverse events (AEs) after FMT were fever and diarrhea, with isolated reports of abdominal pain, small bowel obstruction, cytomegalovirus colitis, pancreatitis, and upper respiratory tract infection. The pooled rate in the adult population of undergoing colectomy after FMT was reported as 7.3%, with authors citing worsening IBD symptoms and increased colon cancer risk in the setting of primary sclerosing cholangitis as the indications for colectomy. Eight deaths were reported in this meta-analysis, one of which was due to aspiration during anesthesia, and seven of which were unrelated to FMT. Tariq et al found variables that may be associated with failure of FMT included severity of CDI, low serum albumin, proton pump inhibitor use, and hypertension. There was insufficient data to carry out a meta-analysis on this subject.

The prospective study by Allegretti et al referenced in the meta-analysis is the largest to date on the subject of CDI and IBD outcomes. In this study, the authors enrolled 50 patients with IBD [15 with Crohn’s disease (CD) and 35 with ulcerative colitis (UC)] and a history of two or more confirmed episodes of CDI within the past year. All patients in the study underwent single FMT delivered via colonoscopy. The primary outcome assessed was FMT failure by week 8 [diarrhea and positive C. difficile stool testing]. If FMT failure occurred, patients underwent a second FMT; C. difficile colonization [no diarrhea but polymerase chain reaction positive for C. difficile] was a secondary outcome. The authors found that 89.8% of patients achieved cure after a single FMT. All four of the patients who initially failed FMT underwent a subsequent FMT, resulting in clinical cure by the eighth week. 91.8% of the patients enrolled were found to have decolonized C. difficile by one-week post-FMT. The authors found that two SAEs occurred, both of which were determined to be unrelated to the treatment, and FMT was otherwise well tolerated. A secondary analysis of the patients in this prospective study found that 62% of those enrolled with UC experienced an improvement in clinical severity and disease activity rating scores, 29.4% experienced no change, and 4% had a flare.

The most recent ACG guidelines note that in patients with IBD who develop recurrent CDI, FMT should be considered, though the quality of evidence is considered very low. Early evidence on the role of FMT in the treatment of CDI in those with concurrent IBD is promising.

Fecal Microbiota Transplantation for the Treatment of Ulcerative Colitis

Recently there has been more research into the role of FMT in the primary treatment of IBD. This research is based on knowledge that the pathophysiology of IBD involves altered intestinal microbiota.

A meta-analysis of four RCTs investigating the role of FMT in the treatment of UC found a pooled rate for clinical remission of 42.1% in the treatment group and 22.6% in the placebo group, with most assessing clinical remission a...
few weeks to months after delivery of FMT. In one of these RCTs, 42% of patients studied had achieved clinical and endoscopic remission 12 months post-FMT.11

There is no clear consensus on dosing of FMT in the IBD population. Parmasothy et al conducted their RCT using intensive dosing (40 infusions of stool blended in saline initially delivered directly to the terminal ileum or cecum via colonoscopy and later self-administered via enema over 8 weeks).10 Others used lower intensity FMT in their RCTs (6 doses of stool blended in water delivered by once weekly retention enemas over 6 weeks12 or 3 doses of stool blended in saline and glycerol initially delivered directly to the right colon via colonoscopy and later administered via enema over 1 week13). It does, however, seem clear that lower dosing employed for the treatment of IBD, which may require multiple doses for effect.

In an RCT analyzing the safety and tolerability of FMT in the UC population, the side effects most associated with FMT delivered via frozen oral capsule were nausea, fever, and a flare of disease requiring steroid taper.25 Delayed side effects have been seen. In another RCT testing the effect of FMT on UC, low-dose FMT delivered colonoscopically and via enema was associated with at least one AE in 51% of participants at 12 months, including worsening colitis requiring colectomy in 13% of patients.11 Notably, 12-month data were considered observational by the authors, as 97% of the control group had crossed over to the treatment group. Two other RCTs on the matter found no significant difference in AEs between treatment and control groups at the 8-week mark.10,12

Pouchitis is inflammation of the ileal pouch, a condition affecting patients with UC who have undergone proctocolectomy. FMT in the management of pouchitis has also been investigated. In a systematic review of four studies (one RCT, one prospective trial, and two cohort studies) by Kayal et al,26 rates of clinical response and remission varied, and FMT in pouchitis was found to be generally safe but ineffective. The authors note that it was difficult to analyze these studies in aggregate given the differing characteristics of the four studies.

**Fecal Microbiota Transplantation for the Treatment of Crohn’s Disease**

Evidence for the use of FMT in the treatment of CD is less robust, though early results were promising. A recent systematic review by Fehily et al analyzed 2 RCTs and 13 cohort studies on this topic, finding that FMT may be an effective treatment option for CD; however, large RCTs are lacking.

In one of the RCTs analyzed in this systematic review, the authors investigated the use of FMT in the treatment of CD over 24 weeks, with the primary outcome of colonization of donor fecal microbiota and with clinical parameters as secondary outcomes. In this RCT, a significant difference was found between the FMT and placebo groups in the reduction in CD severity index at the 6-week time point after FMT.9 Of the 17 patients analyzed, 44% of patients in the placebo group had clinical remission (defined as a score of <5 on the Harvey-Bradshaw Index, a calculator assessing CD severity) at 10 weeks, which dropped to 33.3% at 24 weeks. In the FMT group, 87.5% and 50.0% of patients experienced clinical remission at 10 weeks and 24 weeks, respectively. These, however, were not statistically significant differences. AEs were reported in both treatment and placebo groups, including disease flare; however, the authors did not consider these phenomena to be related to FMT itself.9

**Patient Perceptions on Fecal Microbiota Transplantation**

Patient perceptions of FMT may vary, but most patients are amenable to the procedure after counseling and education. Authors of a 2017 study conducted surveys of FMT perceptions amongst 267 patients in gastroenterology waiting rooms.27 The authors found that those with a university degree were likelier to agree to FMT as compared to those without (p=0.04), suggesting that health literacy may play a role in the acceptance of FMT, and 77% of those surveyed were willing to undergo the procedure if indicated, with respondents’ greatest concerns being lack of hygiene (22%) and risk of disease transmission (30%).

Sentiments on hygiene were echoed in a survey of 95 patients medically managed for UC who were surveyed regarding preferences and concerns surrounding FMT in the management of their IBD.24 In this study, 46% of patients surveyed were willing to undergo the procedure, with 41% citing infection, 24% citing cleanliness, and 18% citing potential to worsen UC as their main concerns regarding FMT.

Patients who have undergone FMT appear to be satisfied with the procedure. In a survey of 54 patients who underwent FMT for recurrent CDI, 96% were willing to recommend FMT to others, and 94% were satisfied with the outcome.29

As the concept of FMT has made its way into the public domain, do-it-yourself (DIY) FMT has emerged – a phenomenon in which the public accesses and administers FMT for various conditions. In a 2019 survey of 84 people who had administered FMT to themselves or others, 43% had performed more than 10 FMTs, with 87% of those surveyed using techniques garnered through the internet.90 92% of these patients surveyed had acquired the DIY stool from a donor known to them. Conditions DIY FMT was used to treat included IBD (35%), IBS (29%), and CDI (26%). Notably, 86% of those with CDI felt that FMT improved their condition, and 90% of those with IBD reported improvement. Some of the reasons cited in this survey for implementing DIY FMT included lack of efficacy of other treatments (64%) or lack of access to physicians offering FMT (33%).
CONCLUSION AND FUTURE DIRECTIONS

FMT is now well-established as an effective intervention in the fight against CDI. In patients with recurrent CDI in the setting of underlying IBD, there is mounting evidence for its high effectiveness and safety. The evidence for FMT as a therapeutic for IBD itself is in its infancy, though with notable potential (Table 1). As FMT continues to gain acceptance, improving access to FMT for both patients and physicians will be necessary.

Table 1. Relative Approximation of the Strength of Evidence for the use of FMT

<table>
<thead>
<tr>
<th>Condition Treated with FMT</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI</td>
<td>+++++</td>
</tr>
<tr>
<td>CDI in patients with IBD</td>
<td>+++</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>++</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>+</td>
</tr>
</tbody>
</table>

Directions for future studies include determining optimal strength, dose, processing conditions, and duration of FMT in the treatment of IBD. Further research is necessary to determine whether the effects of FMT on the treatment of IBD are sustained, or if recurrent FMT is necessary. Future studies will ideally risk stratify patients and provide predictions for which patients with IBD will benefit most from treatment with FMT.

Additionally, the role of individualizing FMT, perhaps by manipulating microbiota, needs further investigation. Live biotherapeutic products (consortia of bacteria or other microorganisms) are an exciting new frontier in the management of CDI and possibly other conditions. This is a topic under active investigation, and may represent a future where the standard of care for IBD extends beyond conventional immunosuppressant therapies.

References


Disclaimer
The views, expressed herein, are those of the authors and do not necessarily reflect the views of the Warren Alpert Medical School of Brown University, Department of Medicine at Alpert Medical School, or Lifespan.

Authors
Sohum A. Patwa, MD, Resident Physician, Department of Internal Medicine, Warren Alpert Medical School of Brown University, Providence, RI.
Christopher Ward, MD, Chief Resident, Department of Internal Medicine, Warren Alpert Medical School of Brown University, Providence, RI.
Colleen R. Kelly, MD, FACC, Associate Professor, Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, RI.

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CRK is a consultant for Sebela Pharmaceuticals.

Correspondence
Sohum A. Patwa, MD
593 Eddy Street, Providence, RI 02903
sohum.a.patwa@gmail.com
ABSTRACT

With the advent of biologic agents, the treatment of patients with Inflammatory Bowel Diseases (IBD) has changed from managing symptoms to achieving remission of disease. Disease remission is associated with better outcomes than symptomatic care alone. The Treat-to-Target paradigm provides targets that serve as surrogates for achieving disease remission. The most important target is endoscopic mucosal healing and other targets include symptomatic response, symptomatic remission, biomarker normalization, and normalization of patient’s quality of life. Targets are reached via utilization of biologic medications that may be modified or substituted as goals are not met. IBD Qorus represents a national collaborative of academic IBD centers and private gastroenterology practices using the Treat-to-Target approach and patient-centered communication methods to provide better care for all patient’s suffering from IBD.

KEYWORDS: IBD; Crohn’s Disease; Ulcerative Colitis; Treat-to-Target; QORUS

Management of patients with Inflammatory Bowel Disease (IBD) underwent a paradigm shift from managing symptoms to a focus on achieving remission, also known as the Treat-to-Target (TTT) approach. TTT was borrowed from rheumatologists and adopted by gastroenterologists to focus on achieving remission of IBD as defined by surrogate markers, chief among them is mucosal healing, and creating goals (targets) that physicians and patients could work together to achieve. This guidance was proposed in the Selecting Therapeutic Targets in IBD program, STRIDE and STRIDE II initiatives by the International Organization for the Study of IBD via systemic review and expert consensus. This method replaces older strategies that focused primarily on controlling symptoms which have not proven to be effective in altering a patient’s disease course. The main goal, or treatment target, of TTT is endoscopic mucosal healing and other targets that are also regularly monitored, which include symptomatic response, inflammatory biomarkers, and overall patient well-being.

Treat-to-Target utilizes the principle that a symptomatic response to treatment does not always result in a decrease in mucosal inflammation; ongoing inflammation may result in complications of IBD such as neoplasia, abscess, and strictures. Mucosal inflammation is quantified endoscopically by mucosal healing, the gold standard outcome for all IBD treatment modalities, as mucosal healing predicts sustained clinical remission and resection-free patient survival. The CALM trial showed that treatment escalation of biologic therapy via symptoms alone led to less mucosal healing when compared to objective measurements, thus providing the foundation for the TTT approach. Furthermore, because assessment of mucosal healing via endoscopy is invasive and expensive, other objective therapeutic targets were needed so surrogate markers of inflammation such as laboratory data were included as targets.

For primary care providers, TTT is likened to monitoring patients with diabetes’ hemoglobin A1c every three to six months and using various tools such as insulin and insulin secretagogues to achieve the goal <7%. While microvascular damage to kidneys, eyes, and peripheral nerves may be present in patients with A1c >7%, they are often asymptomatic. Similarly for patients with IBD, significantly active inflammation may be present while the patient is clinically asymptomatic, thus clinicians should consider changing therapies to achieve treatment targets.

For patients, TTT can be likened to car maintenance. While the check engine light may not be on, and the car is seemingly running smoothly, there still may be hidden problems. By having yearly visits with diagnostic maintenance tests, drivers can determine if there is any significant damage occurring to the car and attempt any measures to alleviate or stop the damage.

The goals for the TTT are achieved primarily through biologic medications, small molecule inhibitors, aminosalicylic acid agents, and immunomodulators in both ulcerative colitis (UC) and Crohn’s Disease (CD). Table 1 shows medications that are commonly used in achieving these targets. Generally, these medications are started at the lowest effective dose and titrated as needed to achieve TTT goals. Another biologic was approved for Crohn’s in late June, 2022: Rizankinumab, a monoclonal antibody targeting IL-23. Several other anti-IL23 inhibitors will become available in the next few years. Table 2 shows a general timeline for achieving the specific targets as defined by the STRIDE-II team.
TREATMENT TARGETS

While not the most important marker for disease progression, symptomatic response is an important patient-centric target for both physicians and patients in the management of IBD. Patients often value symptomatic response above other targets, while mucosal inflammation leading to long-term problems may still be present despite clinical remission. The REACT trial showed that treating to a target of clinical remission generally results in lower rates of surgery, hospitalization, and disease-related complications. The patient-reported outcomes [PRO2] score quantifies and standardizes symptoms of IBD and includes daily stool frequency and abdominal pain for CD and normal stool frequency and absence of rectal bleeding for UC.

### Table 1. Common Medications used in the treatment of IBD

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name(s)</th>
<th>Disease Treated</th>
<th>Major Side Effects</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-tumor necrosis factor agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade, Inflectra, Renflexis, Ixifi, Avasola</td>
<td>CD and UC</td>
<td>Increased risk of bacterial and atypical infections, possibly lymphomas and non-melanoma skin cancer, and worsening congestive heart failure</td>
<td>Contraindicated in patients with NYHA Class III or IV heart failure</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira, Amjevita, Cyltezo</td>
<td>CD and UC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi</td>
<td>UC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Cimzia</td>
<td>CD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Integrin Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Entyvio</td>
<td>CD and UC</td>
<td>No significant increased risk of infections.</td>
<td>Increased risk of Progressive Multifocal Leukoencephalopathy if infected with JC virus (Natalizumab only).</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Tysabri</td>
<td>CD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin-12/23 Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Stelara</td>
<td>CD and UC</td>
<td>Increased risk of infection and possibly non-melanoma skin cancer</td>
<td></td>
</tr>
<tr>
<td>5-Aminosalicylic Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Asacol, Pentasa, Delzicol, Lialda</td>
<td>CD and UC</td>
<td>Allergic reactions, paradoxical diarrhea, and pancreatitis.</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MP/Azathioprine</td>
<td></td>
<td>CD and UC</td>
<td>Bone marrow suppression, hepatotoxicity, pancreatitis, lymphoma</td>
<td>Test for Thiopurine Methyltransferase before use to prevent severe bone marrow aplasia</td>
</tr>
<tr>
<td>Jak Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Xeljanz</td>
<td>UC</td>
<td>Increased risk of infection, lymphoma, thrombosis, and cardiac events</td>
<td></td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>Rinvoq</td>
<td>UC</td>
<td>Increased risk of infection, theoretical risk of perforation</td>
<td></td>
</tr>
<tr>
<td>Sphingosine 1 Phosphate Receptor Modulator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozanimod</td>
<td>Zeposia</td>
<td>UC</td>
<td>Dose dependent decreases in heart rate, increased risk hypertension, associated with increased risk hepatotoxicity, increased risk of infection</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Summary of Short-Term, Intermediate, and Long-Term Targets

<table>
<thead>
<tr>
<th>Short-Term (within 3 months)</th>
<th>Intermediate Targets (within 6 months)</th>
<th>Long-Term targets (6–9 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptomatic response - CD=50% reduction in PRO2 abdominal pain and stool frequency - UC=50% reduction in PRO2 rectal bleeding and stool frequency</td>
<td>1. Symptomatic remission - CD=50% reduction in PRO2 abdominal pain &lt;/=1 and stool frequency &lt;/= 3 - UC= PRO2 rectal bleeding score of 0 and stool frequency of 0 2. Normalization of biomarkers - Fecal calprotectin generally preferred over CRP</td>
<td>1. Endoscopic Healing - Endoscopic remission is preferred 2. Normalized Quality of Life</td>
</tr>
</tbody>
</table>

**TREATMENT TARGETS**

While not the most important marker for disease progression, symptomatic response is an important patient-centric target for both physicians and patients in the management of IBD. Patients often value symptomatic response above other targets, while mucosal inflammation leading to long-term problems may still be present despite clinical remission. The REACT trial showed that treating to a target of clinical remission generally results in lower rates of surgery, hospitalization, and disease-related complications. The patient-reported outcomes [PRO2] score quantifies and standardizes symptoms of IBD and includes daily stool frequency and abdominal pain for CD and normal stool frequency and absence of rectal bleeding for UC.
Table 3. Simplified PRO2 Score for Crohn’s Disease

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>...</th>
<th>Day 7</th>
<th>Average</th>
<th>Weighing Factor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Liquid or Very Soft Stools</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X2</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain (3=severe, 2=moderate, 1=mild, 0=None)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X5</td>
<td></td>
</tr>
</tbody>
</table>

UC (Tables 3 and 4). Symptomatic response is divided into clinical response, a short-term target, and clinical remission, an intermediate target. Clinical response for CD is defined as a 50% reduction in PRO2 abdominal pain and stool frequency and for UC a 50% reduction in PRO2 rectal bleeding and stool frequency by 50%. Clinical remission for CD is defined as PRO2 abdominal pain ≤1 and stool frequency ≤3 and for UC a PRO2 rectal bleeding score of 0 and stool frequency of 0. If clinical response or remission cannot be achieved within 1–2 months for clinical response or 3–6 month for clinical remission, treatment modification should be considered. Given there is a closer correlation between symptomatic response and mucosal healing in UC compared with CD, clinical response is considered a more important target in UC. In addition to symptomatic response, there is also a focus on steroid-free symptomatic remission, decrease in emergency department visits/hospitalization, and other patient-centered goals such as desire for pregnancy.

Endoscopic healing is the most important target in the TTT approach, which is generally defined as no macroscopic injury on direct mucosal imaging via colonoscopy. Mucosal inflammation is associated with poor long-term outcomes, including increased risk of bowel damage and other complications. While endoscopic healing is considered a long-term goal, endoscopic response to treatment can be used to evaluate intermittent responsiveness to treatment in the short term. Generally, a significant decrease in inflammation on colonoscopy is considered endoscopic response, while near complete resolution of inflammation is considered healing. Colonoscopy should be considered six to nine months after starting therapy for CD and three to six months after starting therapy for UC. Sigmoidoscopy can take the place of colonoscopy for UC. Capsule endoscopy or balloon enteroscopy should be considered for CD depending on the anatomic disease location and phenotype.

Histologic healing is not currently a target in the TTT protocol. While histologic remission may result in fewer long-term complications and lower cancer risk in UC, trying to achieve histologic remission has several drawbacks. Sample error can occur in CD depending on biopsy site, inter-reader reliability can vary among pathologists in both diseases, and most importantly, histologic remission is difficult to achieve with an estimated 10% of patients with CD and 33% of patients with UC achieving histologic response despite long-term treatment.

Cross sectional imaging is not a treatment target currently but is a useful adjunct in monitoring disease in IBD. For CD, imaging can find proximal lesions in the small bowel that are not seen on colonoscopy and determine full thickness healing, which may not always correlate with mucosal healing. Popular in Europe and other countries, point-of-care small bowel ultrasound may represent an efficient way to examine for CD or UC flare. Findings that are concerning include increased bowel wall thickness, increased blood flow to segments of bowel, bowel hypomobility, hypoechochogenic bowel wall pattern, and lymphadenopathy. Diagnosis of IBD associated complications such as strictures or fistulas with ultrasound and usage of contrast enhanced ultrasound and elastography represent future directions for managing IBD with ultrasound.

Fecal calprotectin (FC) and C-Reactive protein (CRP) are two important markers of inflammation for patients with IBD as they are objective, non-invasive, and inexpensive. Biomarkers are often obtained post induction, then every six to twelve months throughout the patient’s disease. FC has been shown to predict clinical remission and probability of relapse in patients with CD. The goal for FC in patients with CD is variable, and generally levels greater than 150 μg/g are associated with inflammation. High CRP in patients with CD is associated with higher risk of relapse, while normalization predicts long-term remission. For UC, FC is more sensitive than CRP to predict endoscopic activity and is highly correlated with symptomatic and endoscopic disease. Biomarkers like FC are important adjunctive markers of inflammation and in general correlate with endoscopic inflammation thus providing a noninvasive option. FC is more accurate for colonic inflammation compared with small bowel. However, despite its better performance than CRP, it can have false negatives and/or positives.

To take a holistic approach to IBD care, quality of life and disability have been added as a long-term treatment target.
for patients with IBD. While FC has moderate correlation with patient wellbeing, earlier guidelines did not take patient’s overall quality of life into account. Frequent assessments of patient’s quality of life are now recommended to further elucidate what is important to the patient; thus, there should be a conscious effort to manage factors associated with poorer quality of life such as presence of a stoma, open instead of laparoscopic surgery, and mood disorders. In situations where mucosal healing has been obtained, there are still opportunities for multidisciplinary care with psychiatry, psychology, physical therapy, and social workers in the pursuit of restoring an individual’s quality of life and ensuring a reduction in disability.

**IBD QORUS**

IBD Qorus was developed by the Crohn’s & Colitis Foundation to help develop a therapeutic alliance between patients, providers, and researchers to improve the care of patients with IBD. The mission of the Crohn’s & Colitis Foundation is to, “…find a cure for Crohn’s disease and Ulcerative Colitis while doing everything we can to improve the daily quality of life for patients with inflammatory bowel disease.” IBD Qorus is an electronic platform that allows for collaboration between enrolled gastroenterology clinics and patients. Rhode Island-based GI Associates has been an active participant in IBD Qorus for many years. After a patient consents to participate in IBD Qorus, they are sent a survey before their next appointment. This patient-centered survey was designed to briefly address individual’s symptoms and goals, focusing on what is most important for the patient during their visit. This survey is reviewed by the provider prior to the visit and again during the visit with the patient. By taking the time to complete a survey prior to their visit, patients and providers both come to the visit with clear goals in mind, thus facilitating improved shared decision-making. The end goal of this process is to shift the focus of the appointment away from the disease and towards the patient’s quality of life. The survey also prompts physicians to consider when they should next check for mucosal healing, either via labs or endoscopy, thus also targeting the TTT principles. Furthermore, deidentified data from the surveys populate a database that allows researchers to determine trends in population health.

IBD Qorus utilizes the Institute for Healthcare Improvement Breakthrough Series to achieve quality improvement that can then be widely disseminated. The Breakthrough Series model utilizes Plan-Do-Study-Act (PDSA) cycles after initial in-person learning sessions where promising best practices are widely distributed, and future directions are proposed. There are monthly calls with IBD Qorus staff where PDSA progress and challenges are discussed and addressed jointly.

The data from pre-appointment surveys and PDSA cycles have been used to improve care of IBD patients. For example, low-cost practice changes utilized in IBD Qorus have been shown to decrease unplanned healthcare utilization, and decrease cost by an average of $2,528 per patient. Clinical care pathways for nutritional care and anemia management have also been developed through IBD Qorus. Data is synthesized into reports and sent back to providers who can find clinic-wide trends in data compared with other sites, which can help guide future site directed PDSA cycles. With more than 50 sites nationally, best practices can be shared and benchmarking for important quality issues like steroid use and hospitalization can be examined.

**CONCLUSION**

The TTT approach represents a paradigm shift in improving the quality of care of IBD patients. The TTT approach focuses on endoscopic mucosal healing, inflammatory biomarkers, and overall patient well-being, and not just symptoms to keep IBD in remission. IBD Qorus is a growing network of patients and providers who use the TTT framework to share their experiences and data to further advance IBD care. Future studies are further evaluating clinical outcomes of changing biologic therapy in patients who are otherwise completely asymptomatic with active mucosal disease in efforts to further validate TTT.

**References**


Authors
Daniel Marino, MD, MBA, Department of Internal Medicine, Rhode Island Hospital/Brown University, Providence RI.
Siddharth Singh, MD, MS, Division of Gastroenterology, University of California, San Diego, CA.
Jason Hou, MD, MS, Division of Gastroenterology, Baylor College of Medicine, Houston, TX.
Corey Siegel, MD, Chief, Division of Gastroenterology, Dartmouth Hitchcock Medical Center, Lebanon, NH.
Gil Melmed, MD, Division of Gastroenterology, Cedars Sinai Medical Center, Los Angeles, CA.
Samir A. Shah, MD, Gastroenterology Associates, Chief of Gastroenterology, Miriam Hospital, Providence, RI.

Correspondence
Samir A. Shah, MD
44 West River Street, Providence, RI 02904
Samir_shah_MD@brown.edu
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ABSTRACT

A 67-year-old man presented with a week of flu-like symptoms, hypoxia, and fever. Respiratory viral panel was positive for human metapneumovirus. Initial chest imaging showed left lower lobe opacification, suggesting a bacterial superimposed on viral pneumonia. Despite antibiotics, the patient became tachycardic and increasingly hypoxic, requiring 40 L high-flow nasal cannula. Repeat imaging demonstrated worsening of a left lower lobe process. Elective bronchoscopy with bronchoalveolar lavage revealed hemorrhage. Subsequent autoimmune, bacterial, and fungal workup was negative. The patient was diagnosed with diffuse alveolar hemorrhage (DAH) secondary to human metapneumovirus pneumonia.

DAH is defined as bleeding into the alveolar spaces of the lungs, a process which carries high rates of morbidity and mortality.1 While dramatic in name and often associated with hemoptysis, DAH may only present with clinically subtle and nonspecific features with a variety of alternative etiologies to consider. We present this case of DAH secondary to human metapneumovirus (hMPV) to promote discussion of etiologies of DAH aside from systemic vasculitis.

KEYWORDS: diffuse alveolar hemorrhage, metapneumovirus, anemia

INTRODUCTION

Diffuse alveolar hemorrhage (DAH) can originate from any irritant injuring the alveolar microcirculation. It can manifest with a multitude of clinical findings including progressive anemia, hemoptysis, and acute hypoxic respiratory failure.1 While often associated with systemic vasculitis, there are several other etiologies of DAH which should be considered. There are few literature reports associating hMPV with this life-threatening complication.2,3

CASE

A 67-year-old man with a history of spinal chordoma status post-surgical excision, chronic kidney disease, and neurogenic bladder presented to the Emergency Department with a fever and a home pulse oximeter (SpO2) reading of 84%.

The patient began feeling ill one week prior to admission. Symptoms included drenching night sweats, chills, cough, left upper quadrant abdominal pain, poor appetite, and headaches. He reported progressive worsening of symptoms until presentation. He worked as an engraver and had a sick contact with an individual who had traveled to Florida within two weeks. He denied tobacco or substance use but endorsed consuming one alcoholic beverage daily.

In the Emergency Department, the patient was febrile to 101°F, had a blood pressure of 145/70 mmHg, was tachycardic to 110 BPM, and required 6L of supplemental oxygen to maintain SpO2 at 90%. The patient’s exam was significant for mildly diminished lung sounds in the lower left lung field, mild tenderness noted in the left upper quadrant of his abdomen, and pale appearing skin tone. Labs were notable for hyponatremia (129 meq/L), hypokalemia (3.6 meq/L), elevated creatinine (3.6 mg/dl), mild anemia (hgb 11.6 x10^3 per hpf), and leukopenia (1.6 x10^3 per hpf). Respiratory viral PCR panel was positive for human metapneumovirus. Chest radiograph (Figure 1) on hospital day 1 showed left lower lobe opacification (indicated by the blue arrow), and blunting of the left costophrenic angle (indicated by the yellow arrow).
lower lobe airspace opacification suspicious for pneumonia. The patient was started on broad spectrum antibiotics and bronchodilators.

On hospital day 2 the patient’s fever and tachycardia persisted. Repeat chest radiograph [Figure 2] and CT chest angiogram [Figure 3] revealed bilateral dependent consolidation involving both the right and left lobes. There was no evidence of pulmonary embolism. The patient’s supplemental oxygen requirement increased to 40L. He was continued to be treated as bacterial superimposed on viral pneumonia with antibiotics and supportive care.

The patient’s hemoglobin trended down over four days to 6.8 g/dL. There were no laboratory signs of hemolysis, sequestration, marrow or cell line failure, or nutritional deficits. The patient did not have hemoptysis or gastrointestinal bleeding. The patient underwent elective intubation and bronchoscopy. Bronchoalveolar lavage (BAL) demonstrated incrementally concentrated blood on sequential washes, diagnostic for diffuse alveolar hemorrhage (DAH). Laboratory and pathology studies were performed. Vasculitis, coagulopathy, and autoimmune causes of DAH were excluded. A fungal or bacterial source of infection was not identified. Sputum culture and lavage showed normal respiratory flora. Supportive respiratory measures and broad-spectrum antibiotics were continued. Pulse steroids were also added. By hospital day 14, the patient had improved and was discharged to a rehab facility on 1-2 L of oxygen. Diagnosis on discharge was DAH secondary to hMPV infection.

**DISCUSSION**

hMPV is an enveloped, single-stranded, RNA virus first identified in 2001.³ It spreads via respiratory droplets within a six-ft. radius of an infected individual without proper personal protective gear.⁴ It is a seasonal virus with the highest rate of infection occurring in winter months.¹³ Although predominantly affecting children, elderly, and immunocompromised individuals, studies have demonstrated cases of severe hMPV in immunocompetent adults.⁵⁶ A retrospective study revealed that severe respiratory hMPV led to 1.7% of ICU admission in a hospital located in Spain. The same study also demonstrated increased incidence of hMPV pneumonia in immunocompetent individuals over the last two years of this 10-year longitudinal study (2016–2017).⁴

A typical presentation of hMPV includes fever, cough, pharyngitis, and myalgias. Few case reports of hMPV demonstrate severe pulmonary complications such as DAH.¹ Typically DAH is associated with fungal or bacterial infections rather than viral ones. Treatment is supportive care and management of symptoms when hMPV is the cause.

Most DAH cases are caused by pulmonary capillaritis, occurring when neutrophils invade lung interstitium and necrose the capillaries. This type of DAH is often caused by systemic vasculitis.² The two other types of DAH are known as diffuse alveolar damage (DAD), often occurring in acute respiratory distress syndrome (ARDS), and bland pulmonary hemorrhage from alveolar edema. Definitive diagnosis of the DAH subtypes requires a biopsy of lung tissue to determine histopathology.¹ CT chest imaging can further aid in diagnosis [Figure 3]. Bronchoscopy with bronchoalveolar lavage
with a rising red blood cell count in sequential aliquots from the same anatomical location is the diagnostic standard. Aliquots should be sent for cell counts, gram stain, fungal, bacterial, and viral culture. Once DAH is identified, workup should be tailored to the patient’s presentation and clinical course. As they are often implicated, typical workup of systemic vasculitis includes ANCA, MPO, PR3, anti-GBM, ANA. Although viral respiratory infection is rarely associated with DAH in an immunocompetent host, it is possible as evidenced by the patient presented in this case and should be considered given the implications in guiding treatment.

Clinical determination of virally mediated DAH significantly affects treatment selection. As DAH is commonly inflammatory, corticosteroids and immunosuppressive therapies are standard of care. These are typically initiated upon diagnosis due to high disease mortality. It is of utmost importance to rule out all other explanations for a patient's DAH, especially bacterial or fungal infection, when starting these immunosuppressive medications as they could worsen outcomes. There is currently no antiviral treatment against hMPV, although ribavirin and immunoglobulin G are being explored. The current recommended therapy is supportive, therefore, early identification is crucial to avoid rapidly progressive complications.

A similar case has been reported by Rodriguez et al, both patients presented with tachycardia, hypoxia, and mild anemia with progressively higher oxygen requirements without hemoptysis. Additionally, both patients had a negative autoimmune, vasculitis, and infectious workup other than hMPV. Imaging was also similar, CT angiography demonstrated bilateral multifocal patchy opacities. Our patient’s DAH was discovered relatively early and therefore we were able to intervene before he further decompensated. Unfortunately, the DAH patients described by Rodriguez et al had comparably advanced disease given the reported chest imaging and did not survive the hospitalization.

In summary, this case report demonstrates that while rare, DAH can result from a human metapneumovirus infection. If a patient demonstrates worsening hypoxia, tachycardia, or anemia without evidence of hemoptysis, repeat imaging should still be considered to determine if a bronchoscopy is indicated. It is essential to rule out other causes of DAH such as vasculitis, other autoimmune etiologies, and infections prior to labeling hMPV to determine appropriate treatment. It is our hope this case raises awareness of DAH as a sequela of hMPV to reduce morbidity and mortality.

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Authors
Sarah Anstett, MD, The Warren Alpert Medical School of Brown University, Providence, Rhode Island.
Kristofer S. Gravenstein, DO, MPH, The Warren Alpert Medical School of Brown University, Providence, Rhode Island.
Arkadiy Finn, MD, FACP, FHM, The Warren Alpert Medical School of Brown University, Providence, Rhode Island.
Ibrahem Salloum, MD, The Warren Alpert Medical School of Brown University, Providence, Rhode Island.

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Correspondence
Ibrahem Salloum, MD
Assistant Professor of Medicine, Clinician Educator
The Miriam Hospital Main Building
164 Summit Ave.
Providence, RI 02906
401-793-2104
Fax 401-793-4047
isalloum@lifespan.org


**Brucella Species Staining as Gram-Positive Rod and Gram-Positive Cocci in Chains**

YIGIT BAYKARA, MD; CARLOTTA TRAPASSI, BS; GINA MICELI, BS; CHRISTOPHER BOUCHARD, BS; SARAH BILIDA, BS; JOHN R. LONKS, MD; MARIA MILENO, MD; PARVATHI RADHAKRISHNAN, MD; VALERIE WHITEHEAD, BS; TAO HONG, MD, PhD

**ABSTRACT**

Two cases of Brucellosis were identified at a hospital in Rhode Island. In both cases, the organisms were isolated from the blood cultures. The bacteria did not appear as the classical textbook description of *Brucella* spp. as short, Gram-negative rods; instead, Gram-positive rods and Gram-positive cocci in chains were observed. Due to the atypical Gram stain morphology, *Brucella* spp. were not initially considered as a possible pathogen. Antimicrobial prophylaxes were offered to the technologists who were exposed to the organisms.

**KEYWORDS:** Brucellosis, Brucella, Gram stain, Gram-positive rod, Gram-positive cocci

**INTRODUCTION**

Brucellosis is a zoonotic disease caused by *Brucella* spp. According to the Centers for Disease Control and Prevention (CDC), seventy-three cases were reported in the United States in 2021.1 *Brucella* spp. are short, Gram-negative, non-encapsulated, non-motile, non-spore-forming, slow-growing, facultatively intracellular coccobacilli that are pathogenic to different domestic and wild animals.2,3 Brucellosis can be acquired through ingestion of contaminated food such as unpasteurized dairy products, through skin wounds or mucous membranes after contact with infected animals, or inhalation of the bacteria. Although rare, transmissions from human to human have been reported through different routes.4 Here, we report two cases of Brucellosis that presented to the same emergency department in Rhode Island five days apart with the organisms showing atypical morphology on Gram stain.

**CASE REPORT**

**Case 1**

A 59-year-old male with a past medical history of diabetes mellitus type 2, hyperlipidemia hypertension, atrial fibrillation and transient ischemic attack presented to an emergency department in Rhode Island during March 2022 with subjective fever, malaise, headache, diaphoresis, nausea, left lower quadrant pain and back pain for five days duration.
The organism was oxidase, catalase, and urease positive which matched the expected results for Brucella spp. The laboratory was unable to rule out Brucella spp., so the isolate was sent to Rhode Island Department of Health (RIDOH) for confirmatory testing. The isolate was identified as Brucella spp. by the RIDOH and was sent to CDC for further testing. The isolate was later speciated as Brucella abortus by CDC. Serologic testing was positive for Brucella IgM and IgG. He was treated with doxycycline 100 mg twice a day and rifampin 600 mg once a day (rifampin was chosen due to its availability, ease of administration and lower toxicity). Upon further questioning, the patient admitted consuming unpasteurized milk/cheese while in Aruba. Eight days after presentation, the patient’s symptoms began to improve, and he was discharged on doxycycline and rifampin. He finished the treatment, remained afebrile and was at his baseline health during the six weeks follow-up visit.

Case 2
A 21-year-old female with a past medical history of migraines presented to the same emergency department in Rhode Island with high fever (up to 104.7°F), myalgia, headache, diaphoresis, rhinorrhea, and otalgia for twelve days duration that started just prior to a trip to Puerto Rico. Three months before the illness, she traveled to Sudan for one month and stayed with family and friends. She admitted that she did not take any malaria prophylaxis or follow strict food and water precautions. Blood cultures were drawn on the day the patient presented to the emergency department. She was discharged from the hospital the next day after clinically improving. After approximately fifty hours of incubation, both sets of blood cultures were positive and Gram stain showed Gram-positive cocci in chains. The patient was called back to the emergency department for further work-up and was started on ceftriaxone for bacteremia that was thought to be caused by Streptococcus spp. based on the original gram stain. The organism was identified as Brucella spp. by MALDI-TOF (Vitek MS). The identification was confirmed by RIDOH and was sent to CDC for speciation. The organism was identified as Brucella melitensis by CDC. After diagnosis, the patient was treated with doxycycline 100 mg twice a day for six weeks and gentamicin 240 mg intramuscularly for nine days (she weighed 56.0 kg). The gentamicin was not given on Day 10 since she felt lightheaded; a symptom that might indicate early vestibular toxicity. The patient was discharged from the hospital one week after the initial presentation with follow-up.

DISCUSSION
In a single emergency department in Rhode Island, two cases of Brucellosis presented five days apart. In both cases, the organism did not present with its typical morphology on Gram stain. The organisms appeared as Gram-positive rods or Gram-positive coccii in chains on the original Gram stains. Brucella spp. are known to stain Gram variable or be faintly staining, which can have significant impact on the patient care and safety of laboratory staff. In both cases, the organism presented atypically on Gram stain leading to routine handling of the organism by the medical technologists. In the first case, the organism stained as short Gram-positive rods on the original gram stain (Figure 1) and stained as short Gram variable rods on colony Gram stain (Figure 2). In the second case, the organism stained as Gram-positive cocci in chains (Figure 3). As a part of our laboratory procedure, identification by MALDI-TOF is performed on all organisms that are suspicious for Streptococcus spp. The identification of Brucella spp. was unexpected based on the original gram stain. In both cases, the organisms appeared more consistent with the typical morphology of Brucella spp. after subculture. Due to the atypical Gram stain appearance, Brucella spp. was not initially considered as a possible pathogen in these cultures. Some of the biochemical testing methods were not performed in a Class II biosafety cabinet, which caused some medical technologists in the laboratory to be exposed to the organism. This is significant because Brucella spp. have been known to cause laboratory-acquired infections. Retrospectively, Gram-stain slides from both cases were reviewed by the senior technologists and laboratory director, and the initial results were confirmed. The organisms did stain as Gram-positive. These Gram-stain results were most likely due to the intrinsic nature of the organism rather than a technical error in the Gram-staining procedure. Variable Gram-staining morphology were also identified in cases reported in New York. Antimicrobial prophylaxis was offered to the technologists, and they were monitored by the Employee Health. Lessons learned from these two cases: slow growing organisms from positive blood cultures, regardless of the Gram staining result, should be handled in a Class II biosafety cabinet until Brucella spp. and other highly infectious organisms are ruled out. This is not a standard laboratory practice in most clinical microbiology laboratories; however, laboratories with experience...
of Brucella spp. exposure advocate that this should become a routine laboratory procedure.\textsuperscript{6,7}

Although the incidence of Brucellosis is rare in the northeastern part of the United States, it is still one of the most common zoonotic diseases in developing countries.\textsuperscript{8-10} The rarity of Brucellosis in the United States can easily lead to a misdiagnosis and potentially cause laboratory acquired Brucellosis.\textsuperscript{8,11,12} Brucellosis is one of the most common laboratory-acquired infections and laboratory staff should be aware of the potential for this organism to be recovered in culture despite the low incidence of Brucellosis in the developed countries.\textsuperscript{6} Even though Brucellosis is rare in the United States, the amount of immigration and travel in the United States increases the likelihood that Brucella spp. could be recovered from patients.\textsuperscript{8} In addition to the rarity of Brucellosis, its non-specific symptoms and varying presentations can delay diagnosis and appropriate treatment.\textsuperscript{13} Taking a detailed travel and occupational history as well as questioning consumption of raw or unpasteurized dairy products is vital in the diagnosis of Brucellosis.\textsuperscript{8,13} A thorough investigation is required after Brucella spp. are isolated in the laboratory to identify, notify, and follow up with laboratory staff and healthcare personnel at risk. This includes offering prophylactic treatment to employees who are exposed and monitoring the health of these employees.\textsuperscript{14}

References


Authors

Yigit Baykara, MD, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Carlootta Trapassi, BS, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Gina Miceli, BS, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Christopher Bouchard, BS, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Sarah Bilida, BS, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

John R. Lonks, MD, Division of Infectious Diseases, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Maria Mileno, MD, Division of Infectious Diseases, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Parvathi Radhakrishnan, MD, Division of Infectious Diseases, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Valerie Whitehead, BS, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

Tao Hong, MD, PhD, Microbiology Laboratory, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Rhode Island Hospital, Providence, Rhode Island.

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Correspondence

Tao Hong, MD, PhD, Microbiology Laboratory, 593 Eddy St, APC 11 Providence, RI, 02903, USA. 401-444-3144 thong1@lifespan.org
Delayed Toxic-Hypoxic Leukoencephalopathy After Posterior Reversible Encephalopathy Syndrome

FERNANDO H. IBANHES, BSc; ELIZABETH O’CONNELL, RN, BSN; MAURICIO F. VILLAMAR, MD

KEYWORDS: delayed toxic-hypoxic leukoencephalopathy; delayed hypoxic leukoencephalopathy; posterior reversible encephalopathy syndrome; substance use disorder; toxicology

INTRODUCTION

Delayed toxic-hypoxic leukoencephalopathy (DTHL) is a rare and likely underrecognized clinico-radiological syndrome characterized by white matter damage after hypoxic-ischemic brain injury, usually in the context of toxic exposure.1-3 We describe the unusual case of a patient who developed posterior reversible encephalopathy syndrome (PRES) after two consecutive unintentional drug overdoses, followed by DTHL.

CASE PRESENTATION

A man in his thirties with polysubstance use disorder suffered an unintentional drug overdose after snorting fentanyl-laced cocaine. Upon evaluation by emergency medical services (EMS), the patient had apnea of unclear duration and decreased alertness. Following administration of naloxone, he returned to baseline within minutes. Thirty-six hours later, he had another unintentional overdose. EMS evaluation revealed oxygen saturation of 79% on ambient air and Glasgow Coma Scale of 8. At the emergency department, urine toxicology was positive for amphetamines, cannabinoids, cocaine, and fentanyl. Blood alcohol was undetectable. Non-contrast head CT was normal.

He was hospitalized for management of acute hypoxic respiratory failure [not requiring intubation], acute toxic-metabolic encephalopathy, aspiration pneumonitis, acute tubular necrosis, and rhabdomyolysis. On hospital day 8, he had two generalized tonic-clonic seizures. Same-day non-contrast brain MRI was consistent with PRES (Figure 1). Electroencephalogram revealed moderate, diffuse background slowing with no focal or epileptiform abnormalities. Encephalopathy and metabolic abnormalities gradually improved. Cognition returned close to baseline; however, impaired insight and judgment were present. He remained hospitalized for 40 days, largely from logistics of discharge planning. He had no access to recreational drugs during his hospitalization.

Less than 24 hours after discharge, family members brought the patient from home back to the hospital due to aggressive and disinhibited behavior, and worsening memory. Neuropsychological evaluation showed deficits across a range of functions, including amnestic memory functioning and significant frontal executive impairment. Toxic-metabolic workup, including urine toxicology screen, showed no abnormalities. Non-contrast head CT [not shown] demonstrated interval development of extensive subcortical white...
matter hypodensities. Non-contrast brain MRI (39 days after the initial MRI) now showed extensive, symmetric, and confluent white matter hyperintensities on T2/fluid-attenuated inversion recovery (FLAIR) consistent with DTHL (Figure 2).

A follow-up non-contrast brain MRI (75 days after the initial MRI, not shown), revealed modest reduction in the intensity of white matter lesions. Around the same time, repeat neuropsychological testing demonstrated marked improvement in memory and global functioning from the previous examination, although disinhibition and distractibility persisted. Apparently, the patient was still not back to his premorbid baseline.

**DISCUSSION**

Multiple encephalopathy syndromes can occur from exposure to toxins, and some have characteristic neuroimaging findings. One of these is PRES, which is likely caused by endothelial toxicity or injury. PRES may occur due to use of recreational drugs or certain medications, or from states such as uncontrolled hypertension, eclampsia, or sepsis. Common manifestations of PRES include encephalopathy, seizures, headache, or visual disturbances. MRI commonly shows T2/FLAIR hyperintensities in the parieto-occipital cortices and subcortical white matter, though other areas could be involved. Approximately 2% of PRES patients have concomitant acute toxic leukoencephalopathy, affecting the periventricular white matter. Both PRES and acute toxic leukoencephalopathy are potentially reversible clinicoradiological syndromes.

DTHL is a rare neuropsychiatric syndrome occurring after hypoxic-ischemic brain injury. DTHL has often been described in the context of carbon monoxide poisoning or drug overdose. Its pathophysiology may be related to delayed effects from activation of the apoptotic cascade or dysmyelination following hypoxia. Clinically, DTHL typically follows a “biphasic” clinical presentation: an initial recovery from obtundation or coma gives place to a period of 2–40 days of clinical stability before the abrupt onset of symptoms such as cognitive impairment, upper motor neuron signs, gait disturbance, or psychosis. Given the delay between the acute hypoxic-ischemic event and the onset of neuropsychiatric symptoms, diagnosis of DTHL can be challenging. MRI shows extensive, symmetric, bilateral T2/FLAIR hyperintensities involving the subcortical white matter, sparing subcortical U-fibers. Associated restricted diffusion is common.

![Figure 2. Axial MRI of the brain demonstrating delayed toxic-hypoxic leukoencephalopathy (DTHL). Repeat MRI (39 days after Image 1) revealed resolution of findings consistent with PRES. Instead, there were extensive, symmetric, confluent T2/FLAIR hyperintensities predominantly in the periventricular and subcortical white matter, sparing subcortical U-fibers (top panel). Diffusion weighted imaging (DWI, middle panel) and apparent diffusion coefficient (ADC, bottom panel) showed associated restricted diffusion.](image-url)
Management of DTHL is symptomatic. Many patients experience gradual recovery over 3-12 months. However, “impaired attention or executive function, parkinsonism, or corticospinal tract signs can persist.” To the best of our knowledge, cases of PRES followed by DTHL in the context of recreational drug overdoses have not been previously published.

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Authors
Fernando H. Ibanhes, BSc, The Warren Alpert Medical School of Brown University, Providence, RI.
Elizabeth O’Connell, RN, BSN, The Warren Alpert Medical School of Brown University, Providence, RI.
Mauricio F. Villamar, MD, Department of Neurology, The Warren Alpert Medical School of Brown University, Providence, RI; Department of Medicine, Kent Hospital, Warwick, RI.

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None

Correspondence
Mauricio F. Villamar, MD
593 Eddy St., APC 5
Providence, RI 02903
401-921-7508
Fax 401-736-1057
mauricio_villamar@brown.edu
Metastatic Lung Cancer Presenting as Cutaneous Nodules
THI MY LINH TRAN, MS; AUGUSTUS CHANG, MD; CHAU TRAN; ANDREW HSU, MD

CASE PRESENTATION
A 76-year-old male with a 50-pack-year history of smoking and major depressive disorder presented with a two-month history of loss of appetite, weight loss, fatigue, and palpable masses all over his body. On physical examination, there were multiple diffusely firm, mildly tender, cutaneous and subcutaneous nodules on his chest (Figure 1A), largest in the left axillary area (Figure 1B), his lower back (Figure 1C), shoulders, abdominal area and his groin. CT imaging showed a dominant left perihilar 5.6 x 4.5 cm mass with diffuse cutaneous and subcutaneous masses throughout the chest, abdomen, and pelvis, mediastinal adenopathy, diffuse retroperitoneal metastatic deposits and osseous involvement of the proximal right femoral diaphysis. Biopsy of the cutaneous nodule was consistent with metastatic adenocarcinoma of the lung. Skin metastases indicate late-stage disease and carry a poor prognosis. Two weeks later, he presented to the emergency department with severe hypoxia from obstructive pneumonia complicated by metabolic encephalopathy and stroke. His hospital course was complicated by aspiration pneumonia, hematuria, and deep vein thrombosis in the bilateral lower extremities. After discussing goals of care with family, the patient eventually was transitioned to inpatient hospice. Given the patient’s rapid decline with progressive disease and an overall poor performance status, he was not a candidate for chemotherapy, and passed away a month after his diagnosis.

DISCUSSION
The skin is an uncommon site of metastasis, only found in 0.7–9% of all patients with cancer and typically indicate later stage of disease.1 For lung cancer, metastases are more commonly seen in the brain, bone, liver, and adrenal glands than the skin. Though a rare phenomenon, multiple cutaneous nodules can be the first presenting signs of lung malignancies, found in 1–12% of all cases.2 Therefore, any atypical skin lesions should raise suspicion for lung cancer in patients with extensive smoking history.

References

Figure 1. (A) Multiple cutaneous and subcutaneous nodules identified on patient’s chest; (B) largest cutaneous nodule on the left axilla; (C) multiple subcutaneous nodules identified on patient’s back.
Authors
Thi My Linh Tran, MS, Department of Internal Medicine, The Miriam Hospital, Warren Alpert Medical School of Brown University, Providence, RI.
Augustus Chang, MD, Department of Internal Medicine, The Miriam Hospital, Providence, RI.
Chau Tran, Warren Alpert Medical School of Brown University, Providence, RI.
Andrew Hsu, MD, Department of Internal Medicine, The Miriam Hospital, Providence, RI.

Correspondence
Thi My Linh Tran
thi_my_linh_tran@brown.edu
ABSTRACT
Fewer than 15% of people who have out-of-hospital cardiac arrests survive, but chances of survival can be tripled with effective bystander cardiopulmonary resuscitation (CPR). The majority of states, including Rhode Island, require high school CPR training, yet the impact of this is not well studied. A 33-question REDCap survey regarding cardiac arrest preparedness, CPR education, and barriers to CPR training was emailed to high school staff in Rhode Island. There were 62 responses; 26% reported their school taught CPR and 94% felt it was important for students to have CPR certification. Barriers included time (85%), budget (82%), and materials (79%). Over 80% felt students would not be able to perform high-quality CPR or properly use a defibrillator. Despite laws requiring CPR training and the belief by school staff of the importance of CPR training, the majority of students are not receiving CPR training. Staff report students do not have the ability to perform effective CPR or use a defibrillator.

KEYWORDS: cardiopulmonary resuscitation (CPR) instruction; automated external defibrillator instruction (AED); high school; students; cardiac arrest

INTRODUCTION
Over half a million people each year experience a cardiac arrest in the United States. Less than 15% of people who have an out-of-hospital cardiac arrest survive, but survival can be tripled with bystander cardiopulmonary resuscitation (CPR). Rates of bystander CPR range from 32–61%. Use of automated external defibrillators (AEDs) has also been shown to increase cardiac arrest survival, yet layperson use of AEDs is around 2–7%.

One out of every 250–600 cardiac arrests occurs on school grounds. Both the American Heart Association (AHA) and the American Academy of Pediatrics (AAP) endorse CPR training of school staff and high school students. Currently, 40 states have laws requiring CPR training for high school graduation. In 2013, Rhode Island passed a bill requiring CPR training and an overview of AED use for all high school students. The law requires hands-on practice to support cognitive learning, but formal certification is not required. Similar to many other states, no funding was allocated for the implementation of this law. Teachers in the state of Rhode Island are not required to have CPR certification; however, school nurses and coaches must be CPR-trained.

CPR instruction results in improved knowledge of CPR. A study of 7th–9th grade students who participated in a presentation on basic life support (BLS), a discussion session, and simulated scenarios had significant improvement in BLS skills. In addition, interventions with high school students such as chest compression-only CPR training and brief CPR videos have resulted in students starting chest compressions earlier compared to students who were not trained.

The impact of CPR training laws has not been well studied. One study found people who lived in states with mandatory CPR training for high school graduation were more likely to be trained in CPR, showing a positive effect of training mandates. It is unknown how the legal requirement of teaching CPR and AED use in Rhode Island high schools has been implemented. This study aimed to assess Rhode Island school employees’ perspectives on cardiac arrest preparedness. In addition, it aimed to examine school employees’ perspectives on the training of and barriers to teaching high school students CPR and AED use.

METHODS
Five Rhode Island school districts were contacted via email about participating in a survey study of CPR and AED education. We contacted staff in the four core cities of Rhode Island, which are the cities with the highest percentage of children living in poverty (33%). We focused on these four districts because we felt they would have the greatest number of barriers to teaching CPR. We also reached out to the principal of a fifth school district where the childhood poverty rate was closer to the state average to have survey data from a variety of school districts. Three school districts, out of a total of 32 school districts in the state, agreed to participate in the study, including two core cities and one additional school district. These three districts enroll 26% of the students in the state of Rhode Island.

Between October and November 2020, an online survey was distributed using REDCap. The survey took approximately five minutes to complete. One point person from each district, such as a principal or school leader, forwarded
our brief, anonymous survey to teachers, coaches, administrators, and nurses. The total number of survey invitations sent out is unknown because of how the survey was distributed. As an incentive, participants received a five-dollar Amazon gift card for completing the survey. Consent was obtained at the start of the survey, and respondents answered yes to consent or no to end the survey. Participants were told the purpose of the survey was to understand their experiences with cardiac arrest preparedness in schools and CPR certification for high school students. Participants were informed that responses would be de-identified before use. The survey was anonymous; however, if participants wanted to receive a gift card, their email address was collected for gift card distribution.

INSTRUMENTATION
The survey consisted of 33 questions. The first section focused on respondents’ characteristics, including their role at the school, whether or not they are certified in CPR, reasons they are certified in CPR, and history of witnessing cardiac arrest or performing CPR. The next section focused on questions about schoolwide preparation for a cardiac arrest, such as which adults are CPR-certified and the presence of an AED on the school campus. The third section of the survey focused on student CPR and AED training, such as when CPR is taught in schools, what grade it is taught in, and how it is taught. The last section of the survey asked questions about respondents’ opinions on the importance of CPR training and barriers to CPR training.

DATA ANALYSIS
The data were described using descriptive analyses. Responses about the importance of CPR training were dichotomized into not important (“not at all” or “slightly important”) and important (“moderately important,” “very important,” or “extremely important”). Responses about preparation for cardiac arrest were dichotomized into not prepared (“not at all prepared” or “slightly prepared”) and prepared (“somewhat prepared,” “moderately prepared,” or extremely prepared”). Responses about the agreement with statements were dichotomized into agree (“strongly agree” or “agree”), neutral, and disagree (“disagree” or “strongly disagree”).

IRB Approval
This study was determined to be exempt by the Rhode Island Hospital Institutional Review Board.

RESULTS
A total of 62 responses were collected from teachers (n=46, 74%), coaches (n=9, 15%), school nurses (n=7, 11%), school administrators (n=6, 10%), and others (n=5, 8%).

CPR Training in School Staff
The majority (n=34, 55%) of staff were not CPR-certified. However, the majority of respondents felt it was important for school staff to be CPR-trained, including school CPR instructors (n=61, 98%), coaches (n=60, 97%), administrators (n=60, 97%), and teachers (n=59, 95%). The most common reasons respondents were CPR-certified were: as a job requirement (n=20, 71%), to support job preparedness (n=10, 36%), and to support preparedness for other roles in the community (n=14, 50%). 18% of respondents (n=11) reported CPR has been performed at their school.

Cardiac Arrest Preparedness
The majority (77%, n=48) of respondents reported their school had an AED, which was most often located in the gym (54%, n=26), front office (46%, n=22), or nurse’s office (44%, n=21). 27% of respondents (n=17) did not know if their school had an AED or where the AED was. A minority of respondents reported that their school had a cardiac arrest action plan (n=14, 23%), with most responding “I don’t know” (n=41, 66%). However, 77% (n=48) of those surveyed felt their school was prepared to respond to a cardiac arrest [see Figure 1].

Figure 1. Preparedness of Schools to Respond to a Cardiac Arrest

CPR and AED Instruction in High Schools
One in four respondents reported their school provided training in CPR to students (n=16, see Figure 2), with most responding CPR training was not provided (42%, n=26) or unsure (32%, n=20). Of schools with CPR training, 81% taught CPR in 12th grade (n=13), with CPR being also taught in 11th grade (50%, n=8), 10th grade (25%, n=4), 9th grade (13%, n=2), or after school (1%, n=1). Eighty-one percent taught CPR in health class, but CPR was also taught in physical education (31%, n=5) and elective (25%, n=4) classes. CPR was taught by a variety of instructors, including teachers (69%, n=11), coaches (19%, n=3), and American Red Cross instructors (6%, n=1); 25% (n=4) reported that those who give CPR instruction were officially certified in CPR. The majority of those surveyed reported that the curriculum used to teach CPR was a teacher or instructor self-designed course. CPR instruction was most often done by demonstration, video, or lecture, with only one-third reporting...
hands-on practice. Instruction in AEDs was done in the minority of schools (22%, n=13) and was mainly done using lecture (46%, n=6), video (46%, n=6), and demonstration (46%, n=6). Only 31% (n=4) reported hands-on AED practice.

Importance and Challenges of Teaching CPR and AED Skills

CPR certification for high school graduates was believed to be important by most (94%, n=58). The majority (86%, n=53) disagreed with the statement that most students would be able to perform effective and high-quality CPR until EMS arrived [see Figure 3]. A minority (3%, n=2) of respondents felt students graduated with the confidence to perform CPR. In addition, only 5% (n=3) felt most students would be able to find and properly use a defibrillator. The biggest barriers to training all high school students in CPR were: time (68%, n=42), budget concerns (82%, n=51), and materials to practice (79%, n=48) [see Figure 4].

Open Response to CPR and AED Instruction

Over 50% of respondents answered the free-response question, “Anything else you would like to say about CPR training in high schools?,” and all were positive regarding CPR and AED instruction. Selected responses include:

“It could save a life. I had a brief course many, many years ago in high school but I used it to keep my mother alive when she had cardiac arrest until the EMTs arrived.” —Teacher

“This is a definite need...because of their economic situation our students are less likely to have these trainings.” —Teacher

“This type of training can be highly engaging for students and a gateway into many topics about the human body (anatomy and physiology). We NEED this in our school!” —Teacher

DISCUSSION

This study aimed to assess CPR and AED training in select Rhode Island high schools. Despite state-level laws requiring CPR and AED training, only 26% of respondents reported students are receiving CPR training. Importantly, the majority (94%) felt it was important for students to have CPR certification. Other studies in states which require CPR training for high school students have found that up to two-thirds of school administrators report their school has CPR training, which is higher than what we found in our study. The difference in reporting may be due to who was surveyed, as school administrators may be more likely than other school staff to know what is being taught or may feel pressure to report that state-mandated training is being done. Unsurprisingly, given the low rates of CPR instruction, most staff reported students would not be able to perform effective and high-quality CPR until EMS arrived or find and properly use a defibrillator. These findings highlight the need to increase rates of school CPR training and are an opportunity for local hospitals and community health advocates to partner with schools to offer CPR training, as lack of knowledge has been cited as the number one reason teachers do not feel comfortable teaching CPR.17 Our data support the idea that school staff would be engaged in such training.

In regards to CPR instruction, we found students were most often informally taught CPR, without CPR-certified instructors or state-mandated hands-on practice. In addition, we found that the majority of staff in our study were not CPR-certified, yet 18% reported CPR had been needed
at their school. Although we found low rates of CPR certification, over 95% of those surveyed felt it was important for CPR instructors, coaches, administrators, and teachers to be trained in CPR. At this time, CPR training is not universally required for teacher certification and varies by state. Given that an increasing number of states are mandating CPR to be taught in schools, requiring teachers to become CPR-certified would likely increase the quality of CPR instruction in schools as well as the ability of schools to respond to an on-campus cardiac arrest. A community health initiative that leverages the expertise of local medical trainees such as nursing, physician assistant, and medical students or residents may be one avenue to increase the percentage of CPR-certified students and staff. In addition, training school nurses as CPR instructors may be another way to help increase rates of CPR certification in schools.

Several areas were identified that could positively impact cardiac arrest preparedness. Professional development in schools should focus on making sure staff members are familiar with the location of the school’s AED and ensure an AED is in place, as about one-quarter of those surveyed reported their school did not have an AED. It is impossible to know from this study if respondents simply did not know that their school had an AED or if there is actually no AED present at their school, however, this rate is similar to a study of school nurses which found approximately 28% of schools do not have an AED. In addition, only half of respondents reported their school had a cardiac arrest action plan, suggesting that reviewing an emergency response plan during professional development could support staff members in their comfort with responding to a cardiac arrest.

Lastly, school budget concerns and materials to teach CPR were identified as two of the largest barriers to training all students in CPR, which have been found as barriers in similar studies. Despite overall increasing rates of bystander CPR, time was also cited as an important barrier to teaching CPR. We found a vast variation in what setting as well as with what resources students were taught CPR. A state or national curriculum for teaching CPR and AED with proper use a defibrillator. Further advocacy is needed to increase high-quality CPR until EMS arrived or be able to find and use one defibrillator. Further advocacy is needed to increase rates of CPR certification in schools, professional development could support staff members in their comfort with responding to a cardiac arrest.

CONCLUSIONS

The majority of states, including Rhode Island, have taken the first steps toward improving CPR and AED education by passing mandates for training; however, this study highlights that legislation is not enough. Our study shows that simply passing legislation does not result in compliance with statewide CPR and AED mandates. Unfortunately, our study shows the vast majority of school staff do not believe high school students would be able to perform effective and high-quality CPR until EMS arrived or be able to find and use one defibrillator. Further advocacy is needed to ensure Rhode Island students graduate high school with the ability to perform the lifesaving skills of CPR and defibrillation.

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CONTRIBUTION

Authors

Jessica M. Kelly, MD, MA, Department of Pediatrics, Division of Emergency Medicine, Children’s Hospital of Philadelphia, Philadelphia, PA.

Carly Schmidt, MD, Division of General Pediatrics, Department of Pediatrics, Alpert Medical School of Brown University/Hasbro Children’s Hospital, Providence, Rhode Island.

Robyn Wing, MD, MPH, Department of Emergency Medicine, Alpert Medical School of Brown University/Hasbro Children’s Hospital, Providence, Rhode Island.

Elizabeth Jacobs, MD, Department of Emergency Medicine, Alpert Medical School of Brown University/Hasbro Children’s Hospital, Providence, Rhode Island.

Susan Duffy, MD MPH, Department of Emergency Medicine, Alpert Medical School of Brown University/Hasbro Children’s Hospital, Providence, Rhode Island.

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Correspondence

Jessica Kelly, MD
Children’s Hospital of Philadelphia
Division of Emergency Medicine
3401 Civic Center Blvd
Philadelphia, PA, 19104
215-327-5167
kellyj12@chop.edu
Innovative Approaches to Promoting Health Equity through HIV Prevention in Rhode Island

LILA BHATTARAI, MPH; MEGHAN MACASKILL, MS, MPH; THOMAS BERTRAND, MPH; KATHARINE HOWE, MPH; PHILIP A. CHAN, MD, MS; UTPALA BANDY, MD, MPH

BACKGROUND
The HIV epidemic is an ongoing public health burden in the United States (US) with more than 1.2 million people living with HIV and more than 35,000 new infections each year.1 The impact of the epidemic is not uniformly distributed with certain populations, particularly racial and ethnic minorities and gay and bisexual men and other men who have sex with men (GBMSM), who are at an increased risk for HIV acquisition and suboptimal care and treatment outcomes. Studies have indicated that the most significant predictors for HIV include education, employment, housing, income, and insurance status, with its greatest impacts among the poor, disenfranchised and stigmatized.2 Reducing these inequities presents not only a societal imperative, but a centrally important scientific challenge.

In line with the National HIV/AIDS Strategy for the United States, which provides a roadmap across the nation to accelerate efforts to end the HIV epidemic by 2030, Rhode Island officially adopted the Fast Track Cities “90-90-90” initiative on World AIDS Day in December 2015, as a framework for reducing disparities in HIV testing, treatment and care outcomes.3 The goals of this global initiative are: 1) 90% of people living with HIV know their HIV status; 2) 90% of people who know their HIV-positive status access treatment; and 3) 90% of people in treatment have suppressed viral loads.

In this paper we highlight some of the innovative approaches implemented in Rhode Island that have continued to improve our progress towards the targets set forth by the 90-90-90 initiative (Figure 1).

METHODS
The data presented in this report were obtained from The Enhanced HIV/AIDS Reporting System (eHARS). eHARS data include demographic, lab data, provider reports and information collected through case investigations on all HIV cases in the state. Data was analyzed to examine HIV by race and ethnic categories, by risk groups, and includes data between 2011–2020. Data for Rhode Island’s HIV Care Continuum was derived using Centers for Disease Control (CDC) provided statistical analysis software (SAS) code to calculate the prevalence estimates and care outcomes. All analyses were performed using SAS (version 9.4).

RESULTS
As of 2020, there were an estimated 3,000 people living with HIV/AIDS in the state, including people who have been diagnosed with HIV as well as people living in the community who may be infected, but not yet aware of their HIV status. Over the last 10 years, we identified an average of 73 new cases per year (Figure 2).

Figure 1. Rhode Island HIV Care Continuum, 2019

Figure 2. Number of Newly Diagnosed Cases of HIV, Rhode Island, 2011–2020
The HIV/AIDS epidemic in Rhode Island mirrors national trends, with the population groups most affected being GBMSM, racial and ethnic minorities, and young adults. According to the US Census 2020, 61.6% of Rhode Island populations identified as being White alone, followed by 12.4% Black, and 18.7% Hispanic. When compared to Non-Hispanic Whites, in 2020 the rate of newly diagnosed HIV cases was more than six times higher among Non-Hispanic Black Americans, and more than twice as high among Hispanics/Latinos (Figure 3).

Similar to the minority racial and ethnic groups, the GBMSM population also is at an increased risk for HIV transmission. There were almost three times as many newly diagnosed HIV cases among GBMSM when compared to females, male heterosexuals, and people who inject drugs, combined (Figure 4). In the GBMSM population, the rate of HIV cases in 2020 in Rhode Island was 485 times higher when compared to the rate of HIV cases in heterosexual men.

DISCUSSION

While many social determinants of health present significant barriers to improving HIV care and prevention outcomes, Rhode Island has continued to implement evidence-based strategies, such as routine HIV testing in clinical settings including among pregnant women, partner notification, linkage and return-to-care HIV programs, syringe exchange programs for persons who use drugs, condoms by mail, HIV test kits by mail, and Testing 1-2-3 for HIV/STI testing. As part of surveillance activities, all new HIV diagnoses are interviewed by RIDOH staff to conduct contract tracing and ensure testing of close contacts. Additionally, to foster stakeholder engagement, different partnerships and planning groups have been formed that include social service agencies, AIDS service organizations, community-based organizations, other state agencies, medical providers, and research/academic institutions.

In 1995 the CDC recommended that all physicians counsel pregnant women to get tested for HIV to reduce the risk of HIV transmission to the child, prompted by a report that early use of the antiviral drug zidovudine (AZT), administered during pregnancy, labor, and childbirth to an HIV-positive pregnant woman reduced the risk of HIV infection to the newborn by two-thirds. HIV opt-out screening as part of prenatal care was enacted into Rhode Island General laws in 2009. There have been fewer than five cases of mother-to-child transmission of HIV in the last 10 years in Rhode Island, which can be attributed to the routine HIV testing of pregnant women and timely AZT when indicated, as part of prenatal care.

Needle exchange programs, often called “syringe services programs (SSPs)”, provide a full spectrum of services to individuals who use drugs, including safe injection kits, sharps disposal containers, naloxone, fentanyl test strips, condoms, rapid HIV and hepatitis C testing, and referrals to mental health and social services as appropriate. Since the implementation of the needle exchange program in Rhode Island in 1994, there has been a precipitous drop in new cases of HIV among people who inject drugs, with fewer than six cases reported annually from 2009–2021.
State (ACOS), Project Weber/RENEW, and Parent Support Network operate SSPs throughout Rhode Island though a multi-faceted approach, including three fixed sites, mobile/street-based outreach in core cities, home-delivered services, and most recently harm reduction vending machines. Vending machines are co-located in places that serve high-risk individuals and contain condoms, sterile syringes and other safe injection supplies, fentanyl test strips, naloxone, wound care kits, hygiene kits, and referral cards with resources on them. Further, sterile syringes can be purchased without a prescription at retail pharmacies in Rhode Island. Rhode Island State regulations authorized the opening of harm reduction centers (HRCs), where individuals can utilize pre-obtained substances in a supervised manner for safer consumption; however, as of the time of publication, these facilities are yet to be implemented in Rhode Island.

During the beginning of the COVID-19 pandemic, many individuals experienced increased barriers to accessing condoms, as many of the community distribution locations were closed or limited to the public. Starting in August 2020, individuals could request RIDOH to mail a small package with approximately 15 condoms to their home. Since the program’s inception, RIDOH has provided condoms to over 2,200 individuals representing all 39 cities and towns. RIDOH plans to continue the Condoms by Mail program as there is a consistent demand, and it reaches a population with an otherwise unmet need.

RIDOH-funded community-based organizations, including ACOS, Project Weber/RENEW and AIDS Project Rhode Island (APRI), conduct community-based rapid HIV screening tests. APRI also offers home test kits to further reduce barriers to testing, where individuals can fill out an online form, and receive a rapid HIV test kit in the mail. In 2021, there were 1,202 community-based rapid HIV tests conducted. Approximately 85% of all community-based rapid HIV tests were conducted among individuals who are at high risk of contracting HIV, demonstrating that we are reaching those most in need of testing.

Testing 1-2-3 is a program created by the Rhode Island Department of Health to help asymptomatic Rhode Islanders get tested for HIV and other sexually transmitted infections. The goal is to make the process as easy as possible. Individuals who want to be tested complete a registration form online, go to the lab of their choice to provide urine and blood samples, and then receive their results and follow-up for positive cases. Using this service, individuals can be tested for HIV, chlamydia, gonorrhea, and syphilis. Individuals who use Testing 1-2-3 must have insurance or be able to pay out of pocket, other free clinics are available for uninsured individuals.

The HIV Return-to-Care program, which was implemented by RIDOH in 2013, is a physician-based referral system where dedicated RIDOH staff assist in re-engaging patients in HIV care. Between 2013-2020, RIDOH received 414 provider referrals, of whom 178 individuals were eligible for the program. Among those referred, 53% were determined to be either deceased, incarcerated, already in care, out of state/country or unable to locate and hence, ineligible. More than three-quarters (78%) of all eligible referrals were successfully connected to care through program efforts.

In Rhode Island, every new HIV diagnosis is interviewed to identify partners and refer patients to needed services. In 2020, 504 contacts were identified as needle sharing or sexual contacts from 62 index patients. However, more than 350 of those partners were anonymous and unable to be contacted. While this crucial intervention has prevented numerous high-risk partners from developing HIV through pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), there is still progress to be made on identifying partners of HIV-positive diagnoses. Since 2021, RIDOH started routinely collecting information from newly diagnosed cases about their reason for HIV testing, and the location that they were diagnosed. In 2021, most of the cases were diagnosed at a hospital or emergency department setting. The top reasons individuals were tested for HIV included routine testing, recent condomless sexual encounters, and symptoms of HIV. Collecting this information routinely and uniformly will help inform our prevention efforts by identifying gaps and missed opportunities for early identification of HIV cases.

RIDOH is committed to addressing HIV and achieving 90-90-90 goals. Health equity continues to be a priority to ensure equitable access to HIV care/treatment for all affected groups. Fully addressing HIV in Rhode Island requires collaboration and commitment across public health, clinical, academic, and community-based organizations and institutions.

References
6. All pregnant women advised to get HIV test, consider AZT therapy. AIDS Policy Law. 1995.
8. Testing 1-2-3 can be accessed at: https://www.testing123ri.com/
Authors
Lila Bhattarai, MPH, is Surveillance Manager, Center for HIV, Hepatitis, STD and TB, Rhode Island Department of Health.
Meghan MacAskill, MPH, is HIV Surveillance Epidemiologist, Center for HIV, Hepatitis, STD and TB, Rhode Island Department of Health.
Thomas Bertrand, MPH, is Chief, Center for HIV, Hepatitis, STD and TB, Rhode Island Department of Health.
Katharine Howe, MPH, is Prevention Program Manager, Center for HIV, Hepatitis, STD and TB, Rhode Island Department of Health.
Philip A. Chan, MD, MS, is Consultant Medical Director, Center for HIV, Hepatitis, STD and TB, Rhode Island Department of Health.
Utpala Bandy, MD, MPH, is Interim Director of Health, Rhode Island Department of Health.

Correspondence
Lila Bhattarai, MPH
HIV Surveillance Manager
Center for HIV, Hepatitis, STD and TB
Rhode Island Department of Health
401-222-7539
Lila.bhattarai@health.ri.gov
Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

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<th>VITAL EVENTS</th>
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* Rates per 1,000 estimated population
# Rates per 1,000 live births

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<th>YPLL (c)</th>
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<td>COPD</td>
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<td>374</td>
<td>34.1</td>
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(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.
Adventures

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Capping Prescription Drug Costs: State Initiatives to the Rescue?

ELI Y. ADASHI, MD, MS; I. GLENN COHEN, JD

The ever-rising prescription drug costs in the U.S. constitute an ongoing national challenge that has yet to be addressed by either the executive or legislative branches of the federal government. In recognition of this slow-paced reality, several states have taken to enacting prescription drug pricing transparency laws in the hope of moderating the ever-escalating annual increments. Yet other states elected to affirm the importation of drugs from Canada or to limit the out-of-pocket spending on select medications (e.g., insulin). More recently, however, state legislators set out to impose outright caps on the rising annual state expenditures on prescription drug costs. In this commentary we explore the evolving prescription drug price control strategies at the state level as well as examine the prospects of potential national counterparts thereof.

It has been and remains the implicit policy of the U.S. to grant the pharmaceutical industry a free hand in setting the retail price of prescription drugs absent the advent of negotiation or regulation. Value-based pricing of prescription drugs by a statutorily authorized federal agency, a notion opposed by the pharmaceutical industry, has yet to be taken up by the U.S. Congress. The direct outcome of these hands-off policies has been that the prices assigned to prescription drugs by pharmaceutical companies in the U.S. are uncoupled from both consumer demand and inflation rates. Over the 1980 to 2018 interval, U.S. spending on prescription drugs increased more than tenfold in real terms, that is, independent of inflation. In 2020 alone, the U.S. is estimated to have spent in excess of $350 billion (8.6% of the total national health expenditures) on the procurement of prescription drugs. No other nation comes close to the size of this outlay. Per capita data of the Organisation for Economic Co-operation and Development (OECD) reveal the annual outlays for prescription drugs to be half those incurred by the U.S. The American public is hardly oblivious to these realities. A recent Kaiser Family Foundation poll revealed that “about three in ten say they haven’t taken their medicine as prescribed due to costs.”

Encouraged and enabled by model legislation from the National Academy for State Health Policy, several states took to introducing legislation that would cap the annual prescription drug price increments. At this time, only one such bill, Maine’s LD 1636 [An Act to Reduce Prescription Drug Costs by U.S. International Pricing], was signed into law by Governor Janet T. Mills. Notably, LD 1636 requires the Superintendent of Insurance to create a list of 250 drugs, the price of which is to be “calculated as the lowest cost from official publications of certain Canadian provincial government agencies and the wholesale acquisition cost.” The referenced drugs are “to be dispensed or delivered to a consumer of this State at a cost equal to or lower than the referenced rate. Any savings generated as a result must be used to reduce costs to consumers.” Rhode Island’s Governor Daniel J. McKee, for his part, signed into law legislation which requires insurers to cap the total cost that covered patients pay for insulin at $40 for a 30-day supply. Concurrently, Governor McKee signed into law legislation that prohibits the inclusion of gag orders in pharmacy contracts which preclude pharmacists from offering customers more affordable prescription options. Comparable bills, heretofore introduced in the states of Hawaii, Washington, and Connecticut, have yet to be enacted. The latest example of this legislative trend is the yet-to-be enacted Massachusetts Senate Bill (S. 2774) which seeks to control the state’s “year-over-year increases in pharmacy spend.” Introduced by Governor Charles D. Baker Jr., S.2774 [An Act Investing in the Future of Our Health] proposes an “inflation cap” on prescription drug price accretion. Specifically, the bill sets out to “hold high-cost drug manufacturers accountable through a framework similar to that currently used for payors and providers that exceed the comparable cost benchmark.” In addition, the bill will “penalize manufacturers for excessive drug price increases” and “establish new oversight authority for Pharmacy Benefit Managers [PBMs].” Indications are that the Massachusetts initiative and others like it will be vigorously opposed by the Pharmaceutical Manufacturers of America (PhRMA), the trade group that is representing the U.S. pharmaceutical industry. Early pronouncements of PhRMA relative to the Massachusetts initiative stated that “Massachusetts makes breakthrough medicines. Charlie Baker makes them harder to get.”

Concurrent with the aforementioned state initiatives, the White House sought to address the matter of prescription drug pricing as well. On July 9, 2021, President Biden issued an Executive Order that directed the U.S. Food and Drug Administration (FDA) to “work with states and tribes to safely import prescription drugs from Canada, pursuant to the Medicare Modernization Act of 2003.” The Executive
Order also directed the U.S. Department of Health and Human Services [HHS] “to increase support for generic and biosimilar drugs, which provide low-cost options for patients.” Nary a month later, President Biden called on Congress to lower prescription drug prices by “allowing Medicare to negotiate drug prices, making other needed reforms to lower prices, and building on existing progress to lower the cost of prescription drugs.” Finally, on November 2, 2021, President Biden announced a Prescription Drug Pricing Plan that was to be a part of the Build Back Better Act [H.R. 5376]. Sponsored by John A. Yarmuth [D-KY], the Build Back Better Act calls for authorizing Medicare to negotiate drug prices, imposing a tax penalty if drug companies increase their prices faster than inflation, and lowering the out-of-pocket drug costs for seniors.

The 116th Congress failed to enact a total of 12 prescription drug cost-relevant bills including the Prescription Drug Pricing Reduction Act of 2020, which was sponsored by Sen. Charles E. Grassley [R-IA]. Noteworthy for its focus on the price of prescription drugs under Medicare and Medicaid, the bill “requires drug manufacturers to issue rebates to the Centers for Medicare & Medicaid Services (CMS) for certain drugs covered under Medicare for which the average manufacturer price increases faster than inflation.” The 117th Congress, for its part, revisited but did not enact the Elijah Cummings Lower Drug Costs Now Act [H.R.3] which was sponsored by Frank J. Pallone, Jr. [D-NJ], chairman of the House Committee on Energy and Commerce. The bill “requires HHS to negotiate prices for certain drugs” with manufacturers with inflation caps in mind. Second, the bill insists on “drug price transparency” that is to be required by HHS. Three other bills of relevance to the pricing of prescription drugs, the Freedom from Price Gouging Act [Rep. Katie M. Porter [D-CA]], the Capping Drug Costs for Seniors Act of 2021 [Rep. Steven A. Horsford [D-NV]], and the Drug Price Transparency for Competition Act [DTC] of 2021 [Sen. Richard J. Durbin [D-IL]] failed to advance as well.

With the Build Back Better Act stalled in the Senate, the prospects for near-term congressional action on prescription drug prices appear to be at a standstill. It follows that the legislative momentum on prescription drug prices could well shift to the states. Such a trend is likely to be markedly enhanced if and when Massachusetts, a tried-and-true national health policy bellwether, were to enact Senate Bill S. 2774. Federal legislation intent on holding high-cost drug manufacturers accountable could then follow suit. Whereas progress along these lines would be widely applauded, the historic record does not bode well for congressional action when it comes to the imposition of inflationary limits on drug price increments. To the degree that states comprise a reliable indicator of national trends, the prospect of capping prescription drug prices may have a fighting chance.
The session on examining the lower extremity had gone surprisingly well, considering the masked instructors were doubling as film crew, the students were participating over Zoom, and Celeste, a skeleton, was serving as our patient. As we concluded, I sat Celeste up on the exam table and her skull fell off, landing on the floor with a loud “klonk” easily heard in the nine locations around the United States where our students were sheltering in place.

The moment was ripe with teaching points. The impact had cracked Celeste’s skull directly over the middle meningeal artery, allowing us to observe why that blood vessel can cause such devastating injuries when the lateral skull strikes something hard – in this case, the floor of our examination room.

My mistake set a new bar for the learning errors that mortify beginning medical students. All year my co-teacher and I had emphasized that patient care involves the complex interplay of human relationships, memory, technology, and improvisation. Mistakes are integral to the learning process, rather than occasions for embarrassment or self-rebuke. (Nevertheless, I was experiencing both after beheading my patient and damaging an expensive piece of borrowed equipment in front of my students and colleague.) Still, the comedy of the moment was obvious. “Just modeling that you cannot learn the art and science of medicine without making mistakes,” I remarked, laughing hard.

Although impossible to know at the time, the real takeaway of that afternoon in April 2020 would have nothing to do with Celeste’s accident or the middle meningeal artery, but rather its foreshadowing of the themes of medical education and patient care in the unfolding pandemic.

Altered Connections
Debriefing at the end of class, students and instructors expressed appreciation to be communicating over video despite our far-flung locations, yet we all noted an unfamiliar sense of remove. Reflecting about the difference between screen and in-person connections, we speculated that an invisible energy passes between people sitting together sharing stories, emotions, and human touch. Why does a computer screen prevent that spark?

That afternoon also hinted at the love-hate relationship students, patients, and physicians would develop across the pandemic with video meetings. We’re pleased to connect and communicate but afterward feel like “Zombies,” with tired brains and drained souls, distinct from the physical and emotional fatigue following in-person teaching and patient care. After telehealth days my colleagues and I long for “real patients.”

Seeing their instructors in masks brought home the sobering reality of SARS-CoV-2 to our students. We considered how a patient’s – or doctor’s – mask might alter comfort, communication, and observation. Across the pandemic,
we’ve continued to wonder how masks, goggles, face shields, and gloves will impact student learning and future practice. How best to train students to read non-verbal cues without full facial expressions or teach accurate physical exam skills when institutional guidelines require gloves and limit close examination of the eyes, nose, and mouth?2 Personally, I’ve grown to love the mouth exam – my patient is back momentarily with a full face, smile, tonsils! – reminders of more normal times, relationships, and routines.

**Shifting Boundaries**

Developing new personal and professional boundaries is a fundamental aspect of physician maturation. Remote teaching and patient care blur the usual borders between study, work, and home. “My commute is now six feet,” announced a physician friend.3

In medical school we were taught to bring our patients home with us. At the time I wasn’t quite sure what that meant, but across my career it has grown to embody many imperatives, ranging from calling patients after promising to do so, to reading about their concerns, to handing their problems to the unconscious mind to devise better solutions. While caring for patients from our living rooms and kitchens, bringing home one’s patients takes on a life of its own.

Practicing telemedicine from home during the lockdown, I often felt my patients had moved in, along with a snowballing sense of distraction, worry, and responsibility. They appeared in my dreams. It was hard to stop working. There was always more to do.

Virtual teaching and doctoring require us to slow down, address fewer subjects, explain things clearly, and find creative ways to investigate questions and symptoms. We gain insight into the order or chaos of patients’ and students’ homes and their material wellbeing, relationships, and pets…and vice versa! Sometimes this information brings us closer; at others it blurs patient-doctor, student-teacher, and work-home boundaries.

**Improvisation**

Our improvised class on the lower extremity hinted at the creativity and flexibility we’d need to keep education and patient care going during the pandemic. Ironically, the early days of the pandemic served as a kind of final exam for the disruptive adventure we’d begun about a decade earlier with the arrival of the electronic health record. We have worked to protect the sacred space between patient and physician while integrating the computer, revising job descriptions, and modifying workflows.

Meanwhile, we’ve grown technologically facile in our private lives – texting and video chatting, shopping online, summoning virtual assistants, and employing multiple devices and smartphone apps to get stuff done. So, when the mandates to shelter in place and pivot to remote teaching and doctoring arrived, our brains already harbored a template for the skills of remote work. Over a few short days, medical school classes, meetings, and activities shifted online, and patient care pivoted to telehealth.

**Tolerance for New Mistakes**

All this improvisation also involved a constellation of mistakes. We neglected to schedule a remote patient’s follow-up visit, missed online meetings, bungled video technology, and forgot to unmute. Yet somehow, muddling through this together included a tacit understanding that such mistakes were part of our shared learning curve. Students and patients were remarkably tolerant. We all became more informal and open to testing good ideas regardless of their source. Young helped old, and somehow in the process, the pandemic chipped away at some ossified assumptions and hierarchies in our classrooms, offices, and hospitals.

**Uncertainty**

It has always been challenging to impress upon medical students busy memorizing facts and algorithms that the practice of medicine involves constant uncertainty.4 The pandemic helped ingrain this concept by derailing medical education at every turn.5 In our final meetings during May 2020, students described this realization arriving in waves. SARS-CoV-2 warned them their chosen profession could be dangerous, even life-threatening. The pandemic was going to affect every aspect of their well-planned educations, but in unforeseen ways. Would they ever take off their masks, shake patients’ hands, or share the facial expressions that pass naturally between human beings? Could they plan for the future? How best to fill time back with families of origin and turn this period of enforced exile into something positive for their families, educations, and resumes? These concerns shifted with the news of George Floyd’s death, rising COVID-19 cases, and sobering statistics revealing that most victims were Black, Brown, elderly, or impoverished. Students spoke of a growing sense of responsibility to prepare themselves to take on the second pandemic of structural racism as part of their medical careers. Although we had often mentioned uncertainty as a constant in medicine, here it was in full force.

The students tried to compare COVID-19 to a natural disaster but found it different. After a fire or hurricane, one climbs into the sunlight, surveys the damage, sighs, and gets to work restoring normalcy. The early pandemic, in contrast, more resembled living on Jell-O, with unsteady footing and the constant threat of a crack or meltdown. All assumptions were morphing, but no one knew exactly how.

**The Importance of Humor**

Celeste and her cracked skull reminded us about the value of humor when crossing uncharted territory. One lasting benefit of the pandemic may be taking ourselves less seriously. As our course concluded, medical students and instructors...
joked about shaggier hairstyles and childhood bedroom decorations. We enjoyed selfies of the shorts and flip-flops students sported below the waist even as they appeared on screen in white coats for their final graded patient interview. We were happy to see their playfulness intact, recognizing humor as a powerful tool for healing, especially in lonely and scary times.

**Conclusion**

For more than two and a half years, our viral foe and societal awakening have tested the limits of medical knowledge and dismantled healing and community norms. Yet this painful period has also challenged us to find new ways to connect, learn, and care for patients. Amidst altered relationships, shifting boundaries, and improvisation, we understand uncertainty will be our constant companion. That said, a little tolerance and humor can help us navigate these murky waters and come together to create a more just world for our students and patients.

**Acknowledgment**

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**References**

3. Personal communication, CT Lin, MD.

**Author**

Elizabeth Toll, MD, Professor of Pediatrics and Medicine, The Warren Alpert Medical School of Brown University, Providence, RI.

**Disclosures**

CT Lin, MD, quoted in the essay, read the essay and gave written permission for the quotation to be used.
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**Correspondence**

Elizabeth_Toll_MD@brown.edu
EToll@Lifespan.org
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**NAPLES, ITALY**

Marianne Migliori, RIMJ graphic designer, accessed the journal archives on the rim of the crater at the top of Mount Vesuvius. The ‘Gran Cono’ is currently 2000 feet in diameter and 650 feet deep. Steam continuously escapes through vents in the crater walls.

Mount Vesuvius is an active volcano located on the Gulf of Naples in close proximity to metropolitan Naples. It is considered one of the world’s most dangerous because a population of 3 million reside in its shadow.

The massive eruption of 79 CE buried the Roman towns of Pompeii and Herculaneum under more than 20 feet of ash and pumice. Before that, Vesuvius stood 8000 feet high. The blast reduced it to its current 4200 feet.

Vesuvius still looms over the excavated sites of Pompeii (lower left) and Herculaneum (lower right), which were buried so quickly they were preserved like time capsules.

Its most recent eruption was in March 1944, during World War II, and lasted for 10 days, destroying three nearby villages.

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Council of New England State Medical Societies and New England Delegation to AMA (CNESMS/NED) Fall meeting: Delegates Peter Hollmann, MD, and Alyn Adrain, MD; Alternate Delegates Sara Fessler, MD, and Thomas Bledsoe, MD
New England Delegation to the AMA Political Candidates Meeting: Peter Hollmann, MD

October 4, Tuesday
Office of the Health Insurance Commissioner (OHIC) Administrative Simplification Task Force meeting: Peter Hollmann, MD, Past President; Elizabeth Lange, MD, Past President
RIMS Physician Health Committee [PHC]: Herbert Rakatansky, MD, Chair
Rhode Island Foundation Long Term Health Planning Policy Sub-committee: Stacy Paterno, staff

October 6, Thursday
Meeting with Blue Cross & Blue Shield of Rhode Island (BCBSRI): Thomas A. Bledsoe, MD, President, and Elizabeth Lange, MD, Past President, and staff

October 7, Friday
Rhode Island Health Workforce Planning: Loan Repayment Discussion: Stacy Paterno, staff

October 12, Wednesday
Rhode Island Department of Health (RIDOH) Board of Medical Licensure and Discipline (BMLD): Stacy Paterno, staff
Governor’s Overdose Intervention and Prevention Task Force: Sarah Fessler, MD, Past President
Meeting with Senator Samuel Zurier, American Medical Association – Warren Alpert Medical School Students

October 13, Thursday
Meeting with Neighborhood Health Plan of Rhode Island [NHPRI]: Thomas Bledsoe, MD, President

October 18, Tuesday
OHIC Administrative Simplification Task Force meeting: Peter Hollmann, MD, Past President; Elizabeth Lange, MD, Past President; Stacy Paterno, staff
National Government Services (NGS) 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, Past President
Rhode Island Foundation Long Term Health Planning Policy Sub-committee: Stacy Paterno, staff

October 19, Wednesday
RIDOH Primary Care Physicians Advisory Committee (PCPAC) meeting: Elizabeth Lange, MD, Immediate Past President
Rhode Island Health Workforce Planning: Health Workforce Data Collection & Analytics Workgroup

October 20, Thursday
Executive Office of Health and Human Services (EOHHS) Health Information Technology (HIT) Steering Committee meeting: Stacy Paterno, staff
RIMS leadership meeting with RIDOH Interim Director Utpala Bandy, MD, MPH: Thomas Bledsoe, MD, President; Elizabeth Lange, MD, Past President
RIMS Climate Change and Health Committee

October 24, Monday
Rhode Island Health Center Association annual meeting

October 26, Wednesday
Rhode Island Health Workforce Planning: Health Career Pathways & Pipelines Workgroup
Centers for Medicare & Medicaid Services (CMS) Regional State Medical Society Quarterly meeting

October 27, Thursday
Rhode Island Senate Education Summit
Rhode Island Medical Society – 2nd Congressional District Virtual Forum
RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program.

For more information about group rates, please contact Ali Walz, RIMS Director of Member Services.
Drs. Van Nostrand, Robinson named co-executive directors of URI’s Ryan Institute for Neuroscience

NICOLE MARANHAS
COMMUNICATIONS SPECIALIST AT THE RYAN INSTITUTE FOR NEUROSCIENCE

KINGSTON – WILLIAM VAN NOSTRAND, PhD, and JOHN ROBINSON, PhD, highly regarded for their contributions to neurodegenerative disease research, have been named co-executive directors of the George & Anne Ryan Institute for Neuroscience at the University of Rhode Island, President Marc Parlange announced recently. With a shared vision for the institute’s future, Van Nostrand and Robinson bring a complementary approach to leadership that reflects the successful partnership they have honed during decades of research collaboration.

When Van Nostrand and Robinson answered the call to serve as co-directors of the institute in 2020, the longtime research collaborators did not envision themselves in the roles long term – only long enough to guide the institute during a search for a new executive director. But two heads have proven to be better than one. As co-directors, they not only provided seamless stability through pandemic challenges, but also have moved the institute significantly forward in its research capacity and goals since taking on the roles.

Following an extensive national search, which generated interest from an impressive group of candidates, the selection committee determined that none matched the level of expertise and commitment that Van Nostrand and Robinson bring to the institute.

“What John and Bill have accomplished since joining URI, and particularly in the past two years, is truly remarkable,” said Parlange. “I am confident that, under their leadership, the Ryan Institute and the University are poised for preeminence in the study, prevention, treatment, and, perhaps one day soon, eradication of neurodegenerative disease.”

The Ryan Institute was founded in 2013 with a milestone $15 million gift from Tom and Cathy Ryan and an ambitious mission to treat and prevent Alzheimer’s disease and other neurodegenerative disorders. Van Nostrand and Robinson, who came to URI in 2016 from Stony Brook University, were inspired to make the move to Kingston after seeing the institute’s potential and a closely connected community at URI.

“The focus and vision for the institute strongly appealed to us,” said Van Nostrand, also Herrmann Professor of Neuroscience and a professor of biomedical and pharmaceutical sciences in the College of Pharmacy. “We hadn’t been looking to move, but we were both drawn to the opportunity to be part of something special and help build something new.”

Van Nostrand is considered one of the field’s foremost researchers in cerebral amyloid angiopathy, a condition that commonly occurs with Alzheimer’s disease and holds important clues about the role of brain blood vessels in Alzheimer’s disease and related disorders. Robinson, who holds joint appointments as a professor of psychology in the College of Health Sciences and of biomedical and pharmaceutical sciences in the College of Pharmacy, is a noted behavioral neuroscientist specializing in the use of rodent models to understand nervous system dysfunction and disease. Their work together has helped break new ground in the study of lifestyle factors that may contribute to Alzheimer’s disease and other dementias – a combined expertise that establishes a distinct niche for URI among research institutions.

“John and Bill are talented neuroscience researchers,” said Interim Provost Laura Beauvais. “They are committed to the vision of the Ryan Institute and, along with the early-career faculty they have mentored, have had great success in obtaining external funding to support this research. I have absolute confidence in their leadership, and I look forward to continuing to work with them as they grow the institute.”

The institute also includes a dedicated core faculty whose work investigates under-explored yet critical factors in neurodegenerative disease pathology, as well as an affiliated network of URI faculty with shared research interests. In collaboration with URI’s Interdisciplinary Neuroscience Program and partners such as MindImmune Therapeutics, Inc., a public-private Alzheimer’s disease drug discovery start-up based at URI, the Ryan Institute is part of a vibrant and fast-growing neuroscience community on campus.

“We are both enthusiastic about working with leadership to continue to advance the mission of the institute and expand its reach and impact,” said Robinson. “The institute has made great gains since its start, and we’re eager to leverage those strengths as we begin the next chapter.”

William Van Nostrand, PhD, left, and John Robinson, PhD, have been appointed co-executive directors of URI’s George & Anne Ryan Institute for Neuroscience. [URI PHOTO BY NORA LEWIS]
New suicide prevention research center

**MSU, Henry Ford Health, Brown University to establish new center with $15M NIH grant**

With about one death by suicide reported every 11 minutes in the United States and an increased risk of suicide in individuals involved in the justice system, Michigan State University, Henry Ford Health and Brown University have established the National Center for Health and Justice Integration for Suicide Prevention.

The new suicide prevention research center, also known as NCHATS, is an innovative program funded by a $15 million grant from the National Institutes of Mental Health. The goal is to build information bridges between health care organizations and justice systems to identify individuals at risk for suicide and connect them to care.

The center will examine how to scale successful pilot projects and evaluate both the clinical and cost-effectiveness of suicide prevention activities, said **LAUREN WEINSTOCK**, professor of psychiatry and human behavior at Brown University and the third principal investigator on the grant. “The COVID-19 pandemic and social justice movements of the past several years have brought significant attention to the multitude of inequities faced within the U.S., and particularly how these have contributed to disparities in those who come into contact with the criminal justice system,” Weinstock said. “Amidst calls for decarceration and diversion to mental health and substance use treatment, we need systems in place to effectively identify those who are at greatest risk and connect them to services. With the establishment of NCHATS, we aim to address the all-too-frequent problem in which vulnerable individuals find themselves ‘falling through the cracks’ between the health and justice systems and to connect people to needed care.”

“One of the main problems in suicide prevention is finding people at risk for suicide who are not well connected to health care,” said **JENNIFER JOHNSON**, a principal investigator on the grant and C. S. Mott Endowed Professor of Public Health at Michigan State University College of Human Medicine. “It turns out that many such individuals are in contact with the justice system, including police, courts and local jails. The challenge with connecting individuals in jail with community services is that it is resource-intensive and difficult to do at scale. Our approach solves both problems.”

“These teams bring together the country’s foremost experts to reduce the national suicide rate while establishing interdisciplinary approaches to connect hard-to-reach individuals to care,” said **ARON SOUSA**, dean of the MSU College of Human Medicine. “Public health efforts to identify gaps in care for vulnerable populations are critical to the health of our nation. Together, we can make a lasting difference.”

**BRIAN AHMEDANI**, a principal investigator and director of the Center for Health Policy and Health Services Research and Psychiatric Research at Henry Ford Health, said he and his team are eager to incorporate Henry Ford’s internationally acclaimed suicide research and Zero Suicide prevention program.

“We know that sharing information between institutions is critical to saving the lives of these individuals. This research could also become knowledge that could be applied to the general population, leading to even more lives saved by preventing suicides,” he said.

Justice-involved individuals also have high rates of other suicide risk factors, including mental health problems, substance use, financial challenges, loss of housing, relationship struggles, exposure to violence, and access to lethal means such as firearms, vehicles, or drugs. The justice system and police settings have limited mental health intervention capacity, and health systems are typically unaware of their patients’ justice involvement.

NCHATS includes more than 100 stakeholders, 30 investigators and 15 institutions. The center will use contact with the justice system (e.g., police contact, court involvement, arrest) as a novel indicator of suicide risk in the general population. The center will link big data systems that efficiently track publicly available data on justice involvement to health system records to identify individuals at risk for suicide and connect them to community care.

Even with the known risks, suicide prevention is not the top priority of most police and justice contacts. By bringing together jails, police, health systems/plans, judges and corrections, NCHATS will integrate and expand the public health response to suicide prevention.

The award includes funds for 15 institutions, including:

- Addiction Policy Forum
- Brown University
- Butler Hospital
- CareSource Ohio, Inc.
- Cambridge Health Alliance
- Columbia University
- George Mason University
- HealthPartners Institute
- Henry Ford Health
- Michigan State University
- Mount Auburn Hospital
- Pacific Institute for Research and Evaluation
- Wayne State University
- Education Development Center
- University of Pennsylvania

The full list of partners is available [here](https://www.msu.edu).
RIDOH survey results spotlight health, well-being of RI high school students

PROVIDENCE – While Rhode Island high school students report decreases in the use of some substances, mental health challenges persist for many adolescents in the state, according to new results from the Rhode Island Department of Health (RIDOH)’s Youth Risk Behavior Survey (YRBS).

The YRBS is an optional, anonymous survey conducted every two years in randomly selected Rhode Island high schools to provide a snapshot of how many students are engaging in behaviors or face challenges that may put their physical and mental health at risk. The survey also sheds light on student perceptions of their home and school environments. RIDOH uses these data to develop health programs that address the needs and challenges of Rhode Island youth.

RIDOH collaborates on the YRBS with the Centers for Disease Control and Prevention (CDC), the Rhode Island Department of Education (RIDE), and the Rhode Island Department of Behavioral Healthcare, Developmental Disabilities, and Hospitals (BHDDH). Students in randomly selected Rhode Island high schools responded to the anonymous survey in the fall of 2021. All respondents were in school full time and were not using remote or hybrid learning.

According to responses collected in 2021:

**Substance use**
- 32% of respondents had ever e-vaped (a decrease from 49% in 2019) and 18% reported currently using e-vape products (a decrease from 30% in 2019).
- While alcohol use remained the same as in the 2019 survey, students reported decreases in: Ever smoking cigarettes – Using any type of tobacco product (including cigarettes, cigars, smokeless tobacco, or e-cigarettes) in the previous 30 days and Ever using marijuana and using marijuana during the previous 30 days.
- Students who identified as gay, lesbian, or bisexual (27%) or other/questioning (20%) reported higher rates of e-vaping, alcohol, and marijuana use. Rates of e-vaping and other substance use were higher among female students than males.
- Almost a quarter of 12th grade students who responded to the survey (24%) reported current e-vaping use.

**Mental health**
The 2021 survey results indicate that:
- 38% of students experienced feelings of sadness or hopelessness (up from 32% in 2019). But 22% of students reported receiving the help they needed when feeling anxious or depressed, a decrease from 33% in 2019. Fewer students said they had a teacher or adult at school they could talk to if they had a problem. Survey respondents reported less fighting and bullying on school property, but electronic bullying levels remained the same as they did in 2019.
- Feelings of sadness and hopelessness varied across student demographic groups. Females (52%) were twice as likely as males (25%) to report these feelings. Additionally, students who identified as gay, lesbian, or bisexual (66%) and other/questioning (62%) reported higher rates of sadness and hopelessness than students who identified as heterosexual (29%). Students who did not identify as heterosexual or cisgender also reported higher rates of bullying than students who did identify as heterosexual or cisgender.

**Adverse childhood experiences (ACEs)**
The 2021 survey included two new measures related to adverse childhood experiences (ACEs):
- One in three students (32%) reported that they have lived with someone who was depressed or suicidal.
- One in four students (24%) reported that they have lived with someone who was having a problem with alcohol or drugs.

**Sexual activity, education**
Students who responded to the 2021 YRBS reported a decrease in sexual activity.
- Twenty seven percent of students had ever been sexually active (down from 41% in 2019), while 21% of students said they were currently sexually active (a decrease from 32% in 2019).
- In 2021, fewer students also reported receiving education about sexual health. Of survey respondents, 49% reported being taught about sexually transmitted diseases (STDs) and 56% reported being taught about HIV (a decrease from 72% and 77% in 2019, respectively).
- Five percent of students reported being tested for STDs, a decrease from 15% in 2019.

Link to report: https://health.ri.gov/data/adolescenthealth/
JWU launches accelerated second degree nursing program

**First cohort of four-semester Bachelor of Science program to begin in fall 2023**

PROVIDENCE – Johnson & Wales University will launch an accelerated second degree Bachelor’s of Science in Nursing program after receiving approval from the Rhode Island Board of Nursing Registration & Nursing Education.

“Rhode Island, like the rest of the country, is experiencing a critical shortage of nursing professionals,” said SANDRA G. AFFENITO, PhD, vice chancellor of academic administration. “Between the COVID-19 pandemic and retirements, our health care system has been pushed to its limit. We are proud to offer this program to make nursing more accessible to those interested in a career change.”

The accelerated, four-semester program is intended to be a secondary degree program for students who already completed an undergraduate program with a GPA of 3.0 or higher. To be considered for the highly competitive program, students will have to have completed required prerequisite courses including human anatomy and physiology and chemistry. Otherwise qualified students who do not meet these requirements will have the opportunity to complete the needed classes with a grade of B– or higher at JWU before beginning the nursing program.

Once fully accepted into the program, students will be required to complete in-class instruction, as well as faculty supervised clinical hours through agreements with health care providers across the state.

“Our graduates will be ready to hit the ground running on day one of their career, with real-world experience already under their belt,” said SUZAN MENIHAN, DNP, CNM, JWU’s chief nursing officer and director of the nursing program. “The accelerated timeline will allow us to help meet the needs of Rhode Island’s changing health care landscape.”

As is the case in all health and wellness degree programs offered at JWU, nursing students will be required to complete nutrition coursework, leveraging the university’s culinary strength and history to provide a full-body approach to wellness.

The proposed program was approved by the Rhode Island Board of Nursing Registration & Nursing Education in September.

The new degree program further solidifies Johnson & Wales strong commitment to health care education. In 2014, the university became the first in the state to offer a Physician Assistant Studies Master’s Degree program, and in May graduated the first class of the pioneering entry-level Occupational Therapy Doctorate program, also the first of its kind in the state. Both programs were awarded accreditation, proving their quality in health and wellness education. The university’s decades of hospitality and culinary excellence provide the foundation for JWU’s patient-centered, empathetic, and holistic approach to health care education.

JWU anticipates welcoming the first class of students in fall 2023, with the first graduates concluding their studies by December 2024.

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Nonprofits can apply for $20M in grants to address housing, hunger and behavioral health

PROVIDENCE – Governor DAN MCKEE, Lt. Governor SABINA MATOS, House Speaker K. JOSEPH SHEKARCHI, Senate President DOMINICK J. RUGGERIO and the Rhode Island Foundation recently announced a new $20 million grant program for nonprofits working on food insecurity, housing instability and homelessness prevention, and the behavioral health needs of Rhode Islanders.

The Rhode Island ARPA Support Grants Program targets organizations that experienced negative economic impacts as a result of the COVID-19 pandemic.

The program was created in the Governor’s FY 2023 budget using funding from the state’s $1.1 billion share of the federal American Rescue Plan Act allocation.

The Foundation is accepting applications on a rolling basis until the funding is gone. Grants are expected to range from $50,000 to $150,000. This is the single largest grant program in the Foundation’s 106-year history.

“We will begin immediately to get this funding into the hands of the organizations that are doing the boots-on-the-ground work. We appreciate state leaders having confidence in our ability to provide this funding as these grants will give nonprofits across Rhode Island the resources to help their communities recover from COVID-19’s continuing impact on their daily lives,” said NEIL D. STEINBERG, the Foundation’s President and CEO.

The Foundation will give priority to community-based nonprofits that are located in federally designated low-income neighborhoods.

Applicants must have a federal Employer Identification Number (EIN) and must submit a copy of their most recent IRS Form 990, 990EZ or 990N, and their 501(c)(3) IRS determination letter with their application if it is not already on file at the Foundation.

The Foundation plans to schedule an information session for nonprofits that are interested in applying. For more information about applying for a grant or registering for the info session, visit rifoundation.org.

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Gov. McKee, Congressional delegation kick off construction of new state health lab, major life sciences development

PROVIDENCE – On October 24th Gov. DAN MCKEE was joined by Rhode Island’s Congressional Delegation, legislative leaders, Brown University leaders and healthcare professionals, and development partner Ancora L&G, to break ground on a 212,000 square foot, 7-story building that will house the State’s new health lab, life sciences labs for Brown University, and additional bio-technology space in the state’s Innovation and Design District on the former I-195 land.

“Rhode Island has momentum – and this project is crucial to ensuring the momentum continues in the areas of public health and our life sciences economy,” said Gov. McKee. “We’re grateful for the partners who came together to ensure Rhode Island maximizes this significant economic development opportunity while advancing the state’s important public health goals.”

The Rhode Island Department of Health (RIDOH) State Health Laboratories will anchor the facility, with the remaining floors available to academic and industry partners in the biotechnology field. The 80,000-square-foot state-of-the-art State Health Laboratories will provide updated and flexible space to accommodate biological and chemical testing for a variety of infectious disease, environmental, and forensic testing services.

To help attract additional tenants and encourage a thriving mix of public and private entities focused on health and medicine, Brown University has signed a letter of intent with Ancora to lease 20,000 square feet of laboratory space in the building for a period of 10 years. With 50,000 square feet of direct usable space, the new lab will offer a larger, more modern and technologically advanced workspace than the current state health lab located at 50 Orms Street. Like the Orms Street location, the new lab will include a Biosafety Level 3 facility and will be able to provide critical services for a variety of infectious disease, environmental, and forensic testing needs. The updated space will allow the State Health Laboratory to be more flexible in response to emerging threats and applying new technologies including the expanding field of genome sequencing.

RIDOH State Health Laboratories. The development will deliver much-needed infrastructure for Rhode Island, including state-of-the-art public health labs that will enhance the State’s ability to test for and manage a broad range of infectious diseases and illnesses, together with private-sector lab space to support expansion of the area’s growing bioscience ecosystem. We are excited to be working on this project, demonstrating our ability to deliver against the needs of our anchor institution partners.”

This public/private partnership follows a condominium model with ownership of the State Health Laboratories unit conveyed to the State of Rhode Island on completion, and Ancora retaining ownership of the private laboratory space. Funding for the $81.7 million state laboratory comes from an Epidemiology and Laboratory Capacity Grant from the U.S. Centers for Disease Control (CDC). The total project cost is expected to be $165 million.

Building on its long-standing commitment to supporting Jewelry District projects that contribute to the economic vitality of the city and the state, Brown University has signed a letter of intent with Ancora Partners to lease 20,000 square feet of laboratory space in the building for a period of 10 years. U.S. Senators JACK REED and SHELTON WHITEHOUSE and Congressmen JIM LANGEVIN and DAVID CICILLINE helped secure federal funding for the state health lab in the American Rescue Plan Act (P.L. 117-2) and $81.7 million of this funding was directed to Rhode Island under the Epidemiology and Laboratory Capacity Grant program, which is administered by the CDC. The total project cost is expected to be $165 million.

A groundbreaking ceremony was held Oct. 24th for the State’s new health lab, a seven-story building funded in part by an $81.7M CDC grant. It will also house life sciences’ labs for Brown University, and additional bio-technology space.
Women & Infants to create new labor, delivery center with $5M from Brown

PROVIDENCE – With a $5 million gift from Brown University to support the project, Care New England plans to build a new, technologically advanced labor and delivery center at Women & Infants Hospital that will serve families from Rhode Island and the surrounding region.

In recognition of the gift, CNE will name its state-of-the-art facility the Brown University Labor and Delivery Center when it is completed. It will be designed to meet the specific needs of birthing families and their dedicated medical providers.

SHANNON SULLIVAN, president and COO of Women & Infants Hospital, said that “the new birth center will provide a comfortable and welcoming space that will offer access to high-quality obstetrics for all patients. Rooms will be designed to better accommodate the range of child delivery experiences desired by patients, including meeting the requirements of patient medical conditions. Rooms will be 400 square feet in size, an increase from the current 220-square-foot rooms at Women & Infants, which will not only increase comfort for patients but better accommodate extended family, birth partners and doulas.”

Labor and delivery center rooms will include private baths as well as externally facing windows that permit natural light. In addition, an expanded centralized workspace for physicians and care providers will advance clinical collaboration.

DR. MUKESH JAIN, dean of medicine and biological sciences at the Warren Alpert Medical School, noted that emerging data show a clear link between the health care environment and safe clinical outcomes. For example, labor and delivery units that are designed to facilitate natural childbirth, as those in the new center will be, have lower rates of cesarean delivery and better birth outcomes.

“Women & Infants Hospital is creating an exceptional environment that will advance even further its clinical excellence, and we’re proud to partner with Care New England in caring for the women, children and families of southern New England,” said Dr. Jain, who oversees the medical school’s relationships with affiliated hospitals. “Women & Infants is an integral training site for our medical students, and learning in a facility designed to improve outcomes will impart important lessons in providing patient-centered care.”

CNE expects to begin construction on the Brown University Labor and Delivery Center in early 2023.
Gov. McKee announces new license for Rhode Island State Psychiatric Hospital

New license will position the State to seek up to $40M federal reimbursements for patient care per year

PROVIDENCE – Fulfilling plans announced one year ago, GOV. DAN MCKEE and RICHARD CHAREST, Director of the Department of Behavioral Healthcare, Developmental Disabilities and Hospitals (BHDDH), gathered Oct. 25th on Howard Avenue in Cranston to announce the licensing of a new state psychiatric hospital. Securing the new license will improve patient care and better position the State to seek federal reimbursements that help pay for patient care.

The Rhode Island State Psychiatric Hospital (RISPH), located in the Roosevelt Benton facility, will continue the mission that the Benton facility had as part of Eleanor Slater Hospital – to treat psychiatric and court-ordered forensic patients who have serious mental illnesses.

With the RISPH operating as a standalone hospital, the state will be better positioned to care for psychiatric patients. In addition, the state will be better positioned to seek federal matches that help support patient care within Eleanor Slater Hospital. Based on current patient trends, those additional matches are projected to be, on average, about $30 million to $40 million a year.

“One year ago, we committed to opening a standalone psychiatric hospital as part of our long-term vision for improving our state hospital system, and today we are making good on that commitment,” said Gov. McKee. “This is good news for the patients who need the specialized care that is provided here, and it is good news for our state, because it provides access to available federal dollars that help support the care of our patients.”

“Licensure of the Benton facility as a standalone hospital marks a critical step in our work to transform Rhode Island’s behavioral health continuum of care by preserving and improving access to quality, cost effective healthcare,” said Executive Office of Health & Human Services Acting Secretary ANA NOVAIS.

“This is an important day for Rhode Island and for our state’s healthcare system, and it is made possible by the hard work of many dedicated employees, as well as the support of state lawmakers, state health officials, and other state agencies, and we thank all of them for helping to make this new hospital a reality,” said BHDDH Director Charest. “While the day-to-day operations at Benton will not change, this allows the treatment and care that we provide at Benton to be subject to standards that are more appropriate for psychiatric hospitals, and that will help our staff as they care for our patients.”

“Eleanor Slater Hospital is an essential part of the Rhode Island health system. The separation of the Benton Facility to a standalone psychiatric hospital is an important step in the reorganization of the state hospital that will provide access to critical funds necessary to support quality and safety for both patients and hospital employees,” said M. TERESA PAIVA WEED, President, Hospital Association of Rhode Island.

Operating as a standalone hospital, the Benton facility will continue to treat psychiatric patients, including those who have severe and persistent mental illness and are incompetent to stand trial, those who have been found not guilty by reason of insanity and deemed too dangerous for current release, and those who are serving prison sentences and require specialized treatment not available at the Adult Correctional Institutions.

Licensing the new hospital is one piece of a long-term plan to invest in Rhode Island’s state hospital system. The state budget adopted this year initiates several long-term capital investments, including a new facility on the Zambarano Campus in Burrillville, renovations at the Regan building on the Pastore Campus and the procurement of an electronic medical records system.

At the same time, Eleanor Slater Hospital and BHDDH, with help from the Governor’s Office, the Executive Office of Health and Human Services and the Division of Capital Asset Management and Maintenance, resolved dozens of concerns raised by CMS, The Joint Commission and the State Fire Marshal. The licensing of the new hospital is the latest of these accomplishments.
CNE President, CEO, James E. Fanale, MD, set to retire

Michael Wagner, MD, FACP, named to position

PROVIDENCE – JAMES E. FANALE, MD, president and CEO, Care New England Health System (CNE) will serve his last day at the helm of Rhode Island’s second-largest healthcare system on December 1, 2022, at which time he will retire.

“Working alongside the leadership team at Care New England to improve the quality of healthcare in Rhode Island, while making it more readily accessible and affordable, has been among the highlights of my career. It is truly bittersweet to retire while there is still so much work to be done, however, the time has come for me to pass the torch to someone well-equipped to handle the challenges of operating a healthcare system of this magnitude. I will forever be grateful to those who hold the same vision I do, and that’s to always put patients first, no matter the circumstances,” said Dr. Fanale.

Chairman of Care New England’s Board of Directors, CHARLES REPPUCCI, is thankful to Fanale for his unwavering commitment to healthcare while serving as president and CEO, saying, “During his tenure as president and CEO, Jim faced obstacles that seemed, at times, insurmountable, including financial stresses and national labor shortages, that were a result of the global pandemic. Anyone can lead a ship through calms waters, but it takes a true leader to right it, and stay the course, during unprecedented times, and that’s precisely what Jim did for us. Through it all, Jim persevered and lead with vision and confidence in his plan, and in his hand-picked team, whom he respected. For this, and for so many more reasons, we will forever be grateful to him. I, and the board and staff, wish Jim well in his retirement.”

With that said, Care New England Health System’s Board of Directors prepares to welcome Dr. Fanale’s successor aboard.

After conducting an intensive search, CNE’s Board of Directors has unanimously decided to install MICHAEL WAGNER, MD, FACP, as Care New England’s newest President and CEO, effective December 1, 2022.

Dr. Wagner has built his career and reputation on being a leader who combines his unique experience as a physician, entrepreneur and healthcare executive to transform health care. Throughout his career, he has worked with caregivers in academic and community health care settings across the country.

Dr. Wagner most recently served as Chief Physician Executive (CPE) for Tufts Medicine, a $2.2B leading integrated health system. Tufts Medicine is world-renowned for bringing together the best of academic and community healthcare to deliver exceptional, connected, and accessible care experiences to Massachusetts. As CPE, he led the company’s physician enterprise, which includes the Tufts Medicine Integrated Network, Tufts Medicine Professional Group, and Quality and Patient Safety and Service Lines.

He is also currently President and CEO of the Tufts Medicine Professional Group and Tufts Medical Center Physicians Organization.

During 2019, Dr. Wagner was Interim CEO for Wellforce [now Tufts Medicine], a system recognized for its high quality, lower cost value position and its commitment to keeping care in the community. As Interim CEO, he led the formation of a single obligated group, the selection of a singular EMR platform and drove numerous strategic growth initiatives.

Before that, Dr. Wagner served as President and CEO of Tufts Medical Center, the academic medical center of Tufts Medicine and the principal teaching hospital for Tufts University School of Medicine. During his tenure, Tufts MC achieved a strong financial performance and was twice recognized with a Five Star rating on the Vizient [University Health System Consortium] annual quality and effectiveness evaluation – the only AMC in New England to achieve this recognition.

A magna cum laude graduate of Connecticut College and a graduate of Georgetown University School of Medicine, Dr. Wagner completed his residency and chief residency in Internal Medicine at Dartmouth in Hanover, NH.
**Appointments**

**Drs. Alessandra J. Sax, Jason M. Aliotta join RIMJ’s Editorial Advisory Board**

PROVIDENCE – ALESSANDRA J. SAX, MD, and JASON M. ALIOTTA, MD, have joined the Editorial Advisory Board of the Rhode Island Medical Journal [RIMJ]. They join current members CHARLES A. ADAMS, JR., MD; PHILIP CHAN, MD; STACI FISCHER, MD, and BRETT OWENS, MD.

**Brief bios**

**ALESSANDRA J. SAX, MD,** is an Assistant Professor of Diagnostic Imaging, Clinician Educator at the Alpert Medical School of Brown University and a radiologist at Rhode Island Medical Imaging. She completed a Diagnostic Radiology residency and mini-fellowship in Emergency Radiology at Thomas Jefferson University Hospital in Philadelphia. She also completed her fellowship at Thomas Jefferson University Hospital, where she held a chief fellow position in Musculoskeletal Radiology. Dr. Sax holds both a BS in Neuroscience, cum laude, and a BA in Studio Arts from Brandeis University, Waltham, MA, and an MS in Biomedical Science from Tufts University School of Medicine, Boston. She earned her MD at Boston University School of Medicine.

**JASON M. ALIOTTA, MD,** is an Associate Professor of Medicine at the Alpert Medical School of Brown University. He attended Tufts Medical School and completed a residency in Internal Medicine at the Beth Israel Deaconess Medical Center and a fellowship in Pulmonary and Critical Care Medicine at the Alpert Medical School. Dr. Aliotta joined the faculty of Rhode Island Hospital and The Miriam Hospital in 2006 and currently serves as the Medical Director of the Department of Respiratory Therapy at Rhode Island Hospital and the Associate Medical Director of the Medical Intensive Care Unit at Rhode Island Hospital.

**Vamsy Bobba, MD, joins University Orthopedics’ Center for Spine Health**

EAST PROVIDENCE – University Orthopedics recently announced the addition of VAMSY BOBBA, MD, to the practice’s Center for Spine Health.

Dr. Bobba’s areas of focus include spinal stenosis, degenerative disc disease, herniated discs, instability, deformity, trauma, compression fractures, tumor, and infection. He has extensive experience with in-patient and outpatient procedures, fusions and motion-preserving (non-fusion) procedures, minimally invasive and robotic procedures, disc replacements, and kyphoplasties.

“Each patient’s situation is unique and should be treated as such. It is always my goal to tailor an appropriate plan for each patient’s individual needs, whether surgically or non-surgically, to help restore their quality of life,” Dr. Bobba said. “I am thrilled to join a practice that embraces the same commitment to world-class, comprehensive care as I do.”

After completing his undergraduate years at Columbia University, Dr. Bobba obtained a Master’s Degree from Johns Hopkins University in Bioscience Regulatory Affairs. He then attended medical school at Drexel University in Philadelphia and went on to complete his Orthopaedic Surgery residency at the Detroit Medical Center. Most recently, he completed his spine fellowship at the Warren Alpert Medical School of Brown University.
Edward McGookin, MD, named president of Coastal Medical

PROVIDENCE – EDWARD MCGOOKIN, MD, MHCDS, FAAP, has been promoted from his position as chief medical officer to president of Coastal Medical, which became effective October 20th.

Dr. McGookin practiced general pediatrics for more than 15 years at Coastal Medical Waterman Pediatrics before he assumed the chief medical officer role full-time in 2013.

“Dr. McGookin has lived and breathed Coastal’s values of patient-centered care since joining in 1998, and there is no one more deserving to lead as Coastal’s next president. The future of primary care and population health in Rhode Island is bright under Dr. McGookin’s leadership and vision,” said Lifespan Senior Vice President for Primary Care and Population Health and former Coastal Medical President AL KUROSE, MD.

Dr. McGookin laid the foundation for Coastal’s population health initiatives and built successful clinical programs that have greatly improved patient outcomes, including the clinical pharmacy, diabetes management, heart failure and behavioral health programs. He also spearheaded Coastal’s infection control protocols during the COVID-19 pandemic, helping to keep Coastal patients and employees safe from exposure to the virus.

“Providing patients with access to innovative, high-quality care is what Coastal stands for, and I am humbled to work alongside remarkable colleagues who share the same goal,” said Dr. McGookin. “In this new role, my commitment to enhancing Coastal’s team-based primary care model and Lifespan’s population health strategy will only grow stronger.”

He received his MD from the State University of New York Health Science Center, Syracuse, NY, and completed his residency training in Pediatrics at Hasbro Children’s Hospital in Providence. He also earned a master’s degree in Health Care Delivery Science at Dartmouth College. Dr. McGookin holds an appointment as Associate Clinical Professor of Pediatrics at the Warren Alpert Medical School of Brown University.

He succeeds Dr. Al Kurose, who transitioned to full-time in his role as Lifespan SVP for Primary Care and Population Health after serving as Coastal president since 2008. Dr. Kurose will also serve as chair of the Coastal board.

Patrick L. Green, FACHE, of L+M Healthcare, awarded Senior Health Services Executive of the Year

NEW LONDON, CT/WESTERLY, RI – PATRICK L. GREEN, FACHE, president and CEO of L+M Healthcare, has received the Senior Health Services Executive of the Year award from the National Association of Health Services Executives (NAHSE).

He has over 22 years of well-rounded leadership experience with private not-for-profit health systems and major comprehensive academic health systems. “I humbly accept this award on behalf of all of my fellow healthcare executives and frontline staff who have shown us over the last three years what it looks like to persevere and lead through the most difficult of times,” said Green.

The award, presented at the NAHSE Annual Educational conference in New Orleans recently, recognizes and celebrates the major contributions and efforts of seasoned African American healthcare professionals to the field of healthcare and NAHSE. Green has been president and CEO of Lawrence+Memorial and Westerly hospitals since 2017 and a member of NAHSE for the past 15 years.

NAHSE is a non-profit association of Black health care executives founded in 1968 for the purpose of promoting the advancement and development of Black health care leaders and elevating the quality of healthcare services rendered to minority and underserved communities. ✴
Recognition

National Academy of Medicine elects 100 new members
Among the newly elected regular members is Megan L. Ranney, MD

WASHINGTON, DC – The National Academy of Medicine (NAM) recently announced the election of 90 regular members and 10 international members during its annual meeting. Election to the Academy is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

“This extraordinary class of new members is comprised of exceptional scholars and leaders who have been at the forefront of responding to serious public health challenges, combatting social inequities, and achieving innovative discoveries,” said National Academy of Medicine President VICTOR J. DZAU, MD. “Their expertise will be vital to informing the future of health and medicine for the benefit of us all. I am truly honored to welcome these esteemed individuals to the National Academy of Medicine.”

Among the newly elected regular members is MEGAN L. RANNEY, MD, MPH, FACEP, Warren Alpert Endowed Professor of Emergency Medicine and deputy dean, School of Public Health, and director, Brown-Lifespan Center for Digital Health, Brown University, “for recognition as a national public health leader and communicator who has brought deeper understanding of public health challenges and who has changed public health paradigms through technology-based interventions to reduce violence (particularly firearm injury), mental illness, substance use, and infectious disease risk.”

New members are elected by current members through a process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health. A diversity of talent among NAM’s membership is assured by its Articles of Organization, which stipulate that at least one-quarter of the membership is selected from fields outside the health professions – for example, from such fields as law, engineering, social sciences, and the humanities. The newly elected members bring NAM’s total membership to more than 2,200, including the 190 international members.

Established originally as the Institute of Medicine in 1970 by the National Academy of Sciences, the National Academy of Medicine addresses critical issues in health, science, medicine, and related policy and inspires positive actions across sectors. NAM works alongside the National Academy of Sciences and National Academy of Engineering to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies of Sciences, Engineering, and Medicine also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding of STEMM. With their election, NAM members make a commitment to volunteer their service in National Academies activities.

Help your Patients Keep their Medicaid Coverage

With the Public Health Emergency coming to an end, Medicaid members will need to renew their eligibility with the State of Rhode Island to keep their health insurance.

You can help now by reminding your Medicaid patients to update their account information with their current address and phone number. Medicaid members can update their information by:

• Logging into their HealthSource RI account: https://healthyrhode.ri.gov/
• Calling HealthSource RI at 1-855-840-4774 (TTY 711)

Thank you from all of us at Neighborhood for your commitment and partnership in ensuring Rhode Island families keep their health care coverage!

www.nhpri.org
Recognition

Miriam Hospital recognized by Vizient as 2022 Birnbaum Quality Leadership Top Performer

PROVIDENCE – The Miriam Hospital announces it achieved 9th place out of 148 complex care medical centers/hospitals in the 2022 Bernard A. Birnbaum, MD, Quality Leadership Ranking by Vizient, Inc. The ranking is part of the Vizient Quality and Accountability Study, which rates 650 hospitals and health system against their peers for performance in patient care and safety.

The Birnbaum Quality Leadership Ranking recognizes Vizient members who have demonstrated superior performance in delivering high-quality care, as rated by The Vizient Quality and Accountability Study, which measures quality of patient care across six domains: safety, mortality, effectiveness, efficiency, patient centeredness and equity.

“At The Miriam Hospital we take great pride in our tradition of providing superior patient care, and our commitment to excellence in all that we do,” said MARIA DUCHARME, DNP, RN, NEA-BC, president of The Miriam Hospital. “Our team embraces the belief that everyone is a caregiver – both those in clinical and non-clinical roles. Valuing all contributions has been key to our success in being a consistently high-quality organization.”

The Vizient Quality and Accountability Study rankings factor in measures from composite scoring of patient-level data, and performance data from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey and the U.S. Centers for Disease Control’s National Healthcare Safety Network.

Vizient gives the Bernard A. Birnbaum, MD, Quality Leadership Award annually to its top performing members by organization size/type: comprehensive academic medical centers; large, specialized complex care medical centers; complex care medical centers and community-based medical centers. Complex Care Medical Centers are hospitals and medical centers that perform between 25 and 75 combined cardiothoracic and neurosurgery cases in a year.

The complex care medical center top performers in Vizient’s 2022 Birnbaum Quality Leadership Ranking are:
- Houston Methodist The Woodlands Hospital
- Houston Methodist Baytown Hospital
- Houston Methodist West Hospital
- Penn Medicine Chester County Hospital
- Northwestern Medicine Delnor Hospital
- Houston Methodist Willowbrook Hospital
- Mayo Clinic Health System in La Crosse
- Union Memorial Hospital
- The Miriam Hospital
- Baptist Memorial Hospital - Golden Triangle
- Northwestern Medicine Lake Forest Hospital
- Duke Regional Hospital
- NorthShore Highland Park Hospital
- Northwestern Medicine McHenry Hospital
- Mayo Clinic Health System in Mankato
- UCHealth Poudre Valley Hospital
- Mayo Clinic Health System in Eau Claire

The Vizient Quality and Accountability Study has been conducted annually since 2005. The recognition period is for work spanning July 1, 2021 through June 30, 2022.
Obituaries

HENRY JOSEPH ROBIDOUX, JR., MD, formerly of Barrington, passed away on October 11, 2022.

Henry was a proud veteran of the U.S. Navy, and spent the preponderance of his adult life as a renowned oncology surgeon at Rhode Island Hospital until his retirement.

During his children’s early years Henry coached Barrington youth baseball, hockey, football and volunteered as the Barrington Little League and Barrington High School Football league/team doctor. He spent many years in Barrington politics serving on the town council and involving himself in town organizations. Henry was a kind, gentle and giving soul and will be sorely missed by all that had the honor of knowing and loving him.

He was predeceased by his first wife Anne Marie (Daige) Robidoux, his sister Anne Cody, his son, Mark D. Robidoux and his granddaughter, Amanda M. Robidoux. Henry is survived by his sister Judy Bartlett, by his current wife, Susan Aune, Mark’s wife Susan (Galego) Robidoux and their children; Michael Medeiros, his wife Krystie and their children Bella and Jackson, Daniel Robidoux (wife Leigh), Patrick Robidoux (wife Gina) and Emily Robidoux, by his son John J. Robidoux, his wife Deb and their children; David Robidoux, Bethany (Robidoux) Martin (husband Cliff), Kathryn (Robidoux) Wilcox (husband Tyler) and Dominic Robidoux, by his daughter Mary Kate (Robidoux) Villacres, her husband Gonzalo and their children; Claire Villacres, Anya Villacres and Natalie Villacres, and by his daughter Michelle (Peach) Robidoux and her son Teddy Watson.

In his memory, please consider a donation to his granddaughter Amanda’s charitable organization, Panda’s Helping Paws, 41 Priscilla Drive, Barrington, RI 02806.