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J.M. Shapiro, MD


A.H. Rupawala, MD


S.A. Shah, MD

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Updates in Inflammatory Bowel Diseases, Issue 2

JASON M. SHAPIRO, MD; ABBAS H. RUPAWALA, MD; SAMIR A. SHAH, MD
GUEST EDITORS

Inflammatory bowel disease (IBD) is a set of chronic conditions typically divided into Crohn's disease (CD) and ulcerative colitis (UC). The worldwide incidence of these diseases is increasing at an alarming rate in both children and adults. This has resulted in a robust global research effort aimed at better understanding the immunopathogenesis, natural history, and optimal treatment approach for patients with these complex diseases. In the prior issue of the *Rhode Island Medical Journal* (RIMJ) we presented up-to-date reviews of Preventative Care and Health Maintenance in IBD, Extraintestinal Manifestations of IBD, *Clostridioides difficile* and Fecal Microbial Transplant in Patients with IBD, and Treat-To-Target: The Era of Biologics in IBD Management. We are excited to present the next set of up-to-date review articles authored by a diverse group of national leaders in the IBD field.

INFLAMMATORY BOWEL DISEASE IN CHILDREN AND ADOLESCENTS

A third of patients are under the age of 18 when diagnosed with IBD. Pediatric patients tend to present with more severe disease phenotypes, which places them at risk for unique medical and psychosocial complications. Caring for this delicate patient population involves balancing a number of factors in medical decision making. The accompanying article reviews the epidemiology, clinical presentation, and the management and health maintenance of children and adolescents with IBD, focusing on the importance of a multidisciplinary treatment team. These topics are covered by Dr. Shova Subedi, Associate Director of the Pediatric IBD Center at Hasbro Children's Hospital and Dr. Allison L. Behrle Yardley, attending physician at Hasbro Children's Hospital. The senior author is Dr. Jason M. Shapiro, Director of the Pediatric IBD Center at Hasbro Children's Hospital.

APPROACH TO IBD IN PREGNANCY

The management of IBD in pregnancy involves careful consideration of a myriad of factors in order to optimize the health of mother and child. These include assessment of disease phenotype, surgical history, and medication exposures during pregnancy and thereafter in breastfeeding mothers. Dr. Sumona Saha is a world leader in the field of IBD and pregnancy and prior gastroenterology fellow at Brown University. Dr. Saha is currently Director of Inflammatory Bowel Diseases at the University of Wisconsin School of Medicine and Public Health. She is accompanied by her co-author, Dr. Dana Ley, gastroenterology fellow at the University of Wisconsin.

MANAGEMENT OF HOSPITALIZED PATIENTS WITH ACUTE COLITIS

Patients hospitalized with acute severe ulcerative colitis (ASUC) represent one of the sickest, most challenging IBD phenotypes to manage. Successful treatment involves meticulous, multidisciplinary care, taking a number of clinical variables into consideration. The accompanying article succinctly summarizes the complexity of medical decision making for this unique patient population. Authors include Dr. Abbas H. Rupawala, Director of the Inflammatory Bowel Disease Center at UMass Memorial Medical Center, and Dr. Eric Mao, currently at the University of California Davis and former adult gastroenterology fellow at Brown University. The surgical perspective is covered by Drs. Charles Baldi and Adam Klipfel from the Warren Alpert Medical School of Brown University.

SURGICAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Crohn's disease and ulcerative colitis can present with a range of clinical phenotypes. Optimizing medical management is always a priority, but many patients ultimately require and benefit from surgical interventions. The following article provides a comprehensive, state-of-the art review of surgical management in IBD. Authors of this article include surgical leaders in the field from a variety of institutions, including Dr. Vincent P. Anto and Dr. Andrew R. Watson at the University of Pittsburgh, Dr. Aaron J. Dawes at Stanford University School of Medicine, Dr. Matthew Vrees from the Warren Alpert Medical School of Brown University, and Dr. Amy L. Lightner at the Cleveland Clinic.

NUTRITIONAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Diet is integral to the comprehensive, multidisciplinary management of all patients with IBD. A number of defined diets and dietary therapies have been described as primary and adjunctive treatments of patients with certain IBD subsets. The accompanying, comprehensive article is authored by members of the Pediatric IBD Center at Hasbro Children's Hospital, including: Dr. Rahiya Rehman, a second-year pediatric gastroenterology fellow; Beth Pinkos, RDN, IBD dietitian; Jason M. Shapiro, MD, Director of IBD, and Carolina Cerezo, MD, Chief of Pediatric Gastroenterology, Nutrition and Liver Diseases.

LESSONS FROM THE OCEAN STATE CROHN'S AND COLITIS AREA REGISTRY (OSCCAR)

The Ocean State Crohn's and Colitis Area Registry (OSCCAR) is a prospective, community-based cohort of 408 patients with newly diagnosed inflammatory bowel disease (IBD) in Rhode Island. Enrollment occurred between 2008 and 2013 with prospective follow-up through 2018. The OSCCAR dataset has since served as the substrate for a number of meaningful studies, which are summarized in the accompanying article. Authors for this report include the original principal investigators of OSCCAR, Dr. Bruce E. Sands and Dr. Samir A. Shah. Dr. Sands is currently Chief of Gastroenterology at the Icahn School of Medicine at Mount Sinai and one of the most accomplished international leaders in IBD. Dr. Shah is Chief of Gastroenterology at The Miriam Hospital and recent past president of the American College of Gastroenterology. Neal S. LeLeiko, MD, PhD, was Chief of Pediatric Gastroenterology at Hasbro Children's Hospital when OSCCAR began enrolling patients. He is responsible for the successful enrollment of the majority of new pediatric IBD diagnoses in the state during this time frame. Dr. LeLeiko is currently Director of the Pediatric IBD Program at New York-Presbyterian Morgan Stanley Children's Hospital. Dr. Jason M. Shapiro, current Director of Pediatric IBD at Hasbro, became involved with OSCCAR as a pediatric resident and went on to become site principal investigator of the study in 2015.

COVID-19 AND IBD: LESSONS FROM SECURE-IBD

One of the many challenges posed by the COVID-19 pandemic was assessing the risk of COVID-19 infections in IBD patients, and making decisions around treatment continuation in real time. The SECURE-IBD registry was established by investigators from Mount Sinai Medical Center in New York and the University of North Carolina in Chapel Hill to allow practicing clinicians from all over the world to report disease characteristics and outcomes of COVID-19 infections in their patients with IBD in a deidentified manner. In this article, Dr. Lawrence Kogan, a resident in internal medicine at Rhode Island Hospital and current gastroenterology fellow at Yale, along with Dr. Samir A. Shah, are joined by Dr. Ryan C. Ungaro of Mount Sinai Medical Center in New York, the lead investigator for the SECURE-IBD registry, and Dr. Freddy Caldera from the University of Wisconsin with expertise in vaccinations to COVID. They review data regarding outcomes of COVID-19 infections in patients with IBD, as well as data surrounding immunization for COVID-19 in patients with IBD.

Authors

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

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

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

Correspondence

Jason M. Shapiro, MD

593 Eddy Street, Providence, Rhode Island, 02903

jshapiro@lifespan.org

Inflammatory Bowel Disease in Children and Adolescents

SHOVA SUBEDI, MD; ALLISON L. BEHRLE YARDLEY, MD; JASON M. SHAPIRO, MD

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, immune-mediated condition of the gastrointestinal tract classically labeled as either Crohn's disease (CD) or ulcerative colitis (UC). CD can affect any part of the GI tract from mouth to anus, whereas the inflammation of UC is limited to the colon. IBD can present at any age, from infants to the elderly. Approximately a third of patients are diagnosed during childhood or adolescence.[1] Disease phenotype and clinical course are highly variable, although it has been established that children present with more extensive, complicated disease. In addition to debilitating clinical symptoms, younger patients face the emotional challenges that come with adjusting to a lifelong illness. Caring for children with IBD involves several unique considerations including growth, puberty, bone health, and psychosocial factors that can impact the child and family unit.

EPIDEMIOLOGY

The worldwide incidence of IBD is increasing at an alarming rate, especially in industrialized nations.[2,3] A report from 195 countries found that the United States had the highest global prevalence with nearly a quarter of cases residing here in 2017.[2] A recent systematic review of 130 population-based studies from 48 countries reported a rising incidence and prevalence of pediatric IBD worldwide with a prevalence rate ranging from 28.3 to 63.6 cases per 100,000 in North America.[4] A dramatic rise in children under the age of 6, referred to as very early-onset (VEO) IBD, is also being observed.[5] Recent estimates suggest that VEO-IBD accounts for 15% of pediatric cases.[6] These patients are often very sick with severe disease phenotypes that may not respond to conventional therapies.

PATHOGENESIS

The immunopathogenesis of IBD has been attributed to a combination of causative factors including genetic predisposition, defects in the innate and adaptive immune system, alterations of the gut microbiome and various environmental exposures.[7,8] Genome-wide association studies (GWAS) have identified over 200 host susceptibility loci to date.[9] These genetic polymorphisms are associated with a variety of immune-mediated pathways within the mucosal immune system. Family history of IBD is noted in about 12% of patients and susceptibility risk is increased in those with an affected first-degree relative.[10] The concordance rate among monozygotic twins is reported to be approximately 15% and 35% for CD and UC, respectively.[11] Thus, genetic predisposition is insufficient to explain disease onset and several environmental risk factors have been identified.

Environmental risk in IBD seems to be driven by factors influencing the gut microbiome. At steady state the intestinal microbiota is comprised of trillions of bacteria, viruses, protozoa, and fungi. A number of chronic diseases have been associated with alterations in the delicate balance of this ecosystem, referred to as dysbiosis. Whether the dysbiosis observed in IBD is primary or secondary to the underlying intestinal inflammation is still not clear.

The adult microbiome is set during the first 3 years of life. Early life events such as birth method, breastfeeding, and exposure to antibiotics have been shown to impact microbiome development. A landmark study showed that the microbiome of healthy individuals living in industrialized nations (the United States) had a markedly less diverse microbiome compared to those residing in under-developed rural communities in Africa and Venezuela.[12] IBD is generally a disease of western civilization with increasing incidence noted in newly industrialized nations, suggesting that this baseline lack of microbial diversity driven by our environment is likely itself an important risk factor. One possible explanation of this phenomenon is termed the hygiene hypothesis. This presupposes that industrialization, improved hygiene and lack of enteric pathogen exposures may increase risk of developing certain immune-mediated conditions, including IBD.[13]

CLINICAL PRESENTATION

Children with IBD can present with a variety of signs and symptoms. The majority will present with a combination of gastrointestinal complaints including abdominal pain, nausea, vomiting, diarrhea or hematochezia. Patients with UC typically have blood in the stools at presentation. Significant proctitis or inflammation of the rectum is commonly seen in UC. This can result in debilitating symptoms such as urgency, tenesmus and nocturnal stooling. Younger children

with CD are more likely to have colonic involvement and the initial presentation can mimic UC. The majority of older children and adolescents with CD have inflammation to varying degrees in the terminal ileum and colon at presentation. These patients can present with a spectrum of symptoms related to the disease location.

Weight loss and delayed linear growth is especially concerning in pediatric IBD. Studies suggest that growth failure occurs in approximately 40% and 10% of children with CD and UC, respectively.[14,15] Increased metabolic demand, poor oral intake, malabsorption, corticosteroid therapy, and growth hormone resistance due to chronic inflammation are potential contributing factors. Review of an accurate growth chart is critical as children can present with an indolent decline in growth velocity and/or weight percentiles well before symptom onset. Co-morbid obesity should not dissuade further evaluation when clinically indicated. Recent reports suggest that approximately 30% of children with IBD are obese at the time of diagnosis.[16]

Up to 30% of children with IBD experience extra-intestinal manifestations (EIMs).[17] These are reviewed in a separate article.

EVALUATION

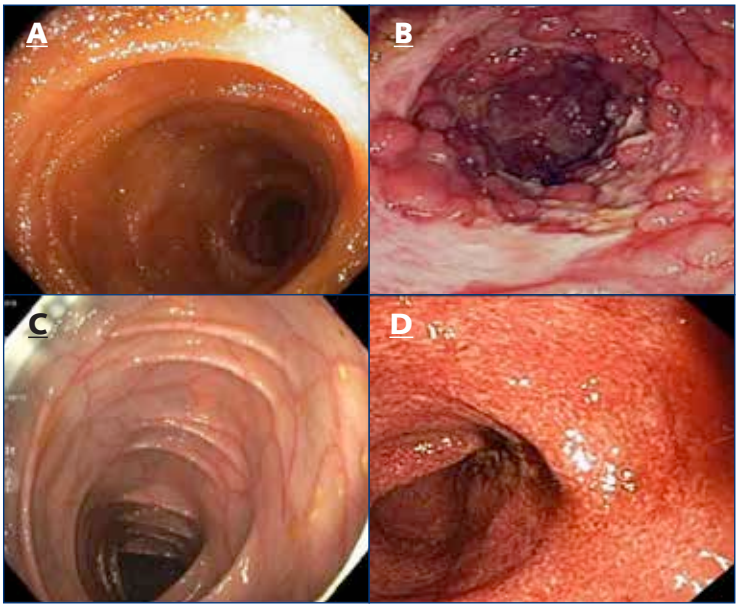
The diagnosis of IBD is based on a combination of clinical, serologic, endoscopic, pathologic and radiographic data. Initial evaluation should involve a thorough history, physical exam and review of outpatient growth charts. Pubertal assessment via Tanner staging should be completed, when appropriate. A supervised perianal inspection should also be performed to assess for possible perianal skin tags, fistulae or abscesses. Digital rectal exam is rarely required in children with suspected IBD.

Table 1. Laboratory Evaluation of IBD

Blood	Anemia, low mean corpuscular volume, leukocytosis, thrombocytosis Hypoalbuminemia: chronic malnutrition, intestinal inflammation, malabsorption Iron deficiency: chronic inflammation, malnutrition Elevated ESR and CRP Elevated Liver enzymes Genetic test: r/o monogenic IBD in VEO-IBD Immune deficiency work up: r/o immunodeficiency condition in VEO-IBD Antibody test: pANCA, ASCA, Anti-Cbir, Anti-Ompc1 -No initial diagnostic role -Could predict disease behavior and disease severity Serum trough and antibody level (Biologics): help optimize treatment
Stool	Salmonella, Shigella, Campylobacter, Yersinia, Escherichia coli 0157:H7 Clostridium Difficile: frequent monitoring and aggressive treatment indicated Fecal calprotectin &lactoferrin

pANCA: Antineutrophil Cytoplasmic Antibodies
ASCA: Anti-Saccharomyces Cerevisiae (ASCA) Antibodies

Figure 1: Endoscopic views of healthy tissue compared with inflammatory bowel disease. **A.** Normal terminal ileum. **B.** Crohn disease with patchy inflammation, cobble stoning, deep ulcers, exudates, altered vascular pattern and friability. **C.** Normal colonic mucosa with intact architecture and vascular patter. **D.** Ulcerative colitis with continuous, uniform inflammation.



Laboratory tests to assess for signs of inflammation and disease chronicity are often the first step in evaluation (**Table 1**). Up to 20% of children can present with normal laboratory values.[18] Thus, normal blood work should not deter further evaluation when clinically indicated. Esophagogastroduodenoscopy (EGD) and Ileo-colonoscopy with biopsies provide detailed evaluation of mucosal inflammation and distribution (**Figure 1**). In certain cases, advanced endoscopic techniques such as single- and double-balloon and spiral enteroscopy can assess the mid-small bowel, which is otherwise inaccessible via standard endoscopic approaches. These advanced procedures are rarely indicated in pediatric patients. Video capsule endoscopy (VCE) is another way to evaluate the small bowel and can be completed in most children, when indicated. Magnetic resonance enterography (MRE) and computerized tomography enterography (CTE) are the preferred imaging modalities to assess for small bowel involvement in CD. These cross-sectional images also assess for complicated disease behavior such as intestinal strictures, fistulae and abscesses. An MRE is preferred due to lack of radiation exposure, although these are long study protocols which younger children may not be able to tolerate. A bone age study, via radiograph of the hand, is frequently utilized in children to assess the degree of growth impairment. Bone mineral density analysis via dual-energy x-ray

absorptiometry scan (DEXA) should be considered in children at risk for low bone mineral density, especially in those with prolonged corticosteroid (CS) exposures. The workup for younger children with VEO-IBD involves genetic testing to rule out monogenic causes and underlying immunodeficiency syndromes that can result in an IBD-like phenotype. Thus, all children under the age of 2 with suspected IBD should have genetic testing prior to starting immune-modulating medications. Such genetic testing is commercially available as a monogenic IBD gene panel which is offered by laboratories such as Invitae and the Mayo Clinic. Additionally, genetic testing is available through VEO-IBD research consortia at centers across the country.

DISEASE CLASSIFICATION

IBD is classified into CD, UC and IBD- unclassified (IBD-U). IBD-U is typically reserved for patients with colonic inflammation that may not completely meet diagnostic criteria for either CD or UC. Disease phenotype and behavior is classified in adults according to the Montreal Classification schema.[19] This does not take into account important pediatric-specific factors. Thus, the Paris Classification is used in children.[20] This tool includes more detailed description of disease phenotype and behavior while incorporating assessment of patient age and growth. Side-by-side comparison of the Montreal and Paris Classifications for CD and UC are presented in **Tables 2**,**3**.

Table 2. Montreal and Paris classification of CD

CHARACTERISTICS	MONTREAL	PARIS
Age At Diagnosis	A1: <17 yrs. A2: 17-40 yrs. A3: >40 yrs.	A1a: 0 to<10 yrs. A1b: 10 to <17 yrs. A2: 17 to 40yr A3: >40 yrs.
Location	L1: Terminal ileal +/- limited cecal disease L2: Colonic L3: Ileocolonic L4: Isolated track disease	L1: Distal 1/3 ileal +/- limited cecal disease L2: Colonic L3: Ileocolonic L4a: Upper disease proximal to LoT L4b: Upper disease distal to LoT and proximal to distal 1/3 ileum
Behavior	B1: Non-stricturing and Non-penetrating B2: Stricturing B3: Penetrating P: perianal disease modifier	B1: Non-stricturing and Non-penetrating B2: Stricturing B3: Penetrating B2/B3: Both penetrating and structuring disease P: perianal disease modifier
Growth	NA	G0: No evidence of growth delay G1: Growth delay

*LoT: Ligament of Treiz

Table 3. Montreal and Paris classification of UC

CHARACTERISTICS	MONTREAL	PARIS
Extent	E1: Ulcerative proctitis E2: Left Sided UC (distal to splenic flexure) E3: Extensive (proximal to splenic flexure)	E1: Ulcerative proctitis E2: Left-Sided UC (distal to splenic flexure) E3: Extensive (distal to hepatic flexure) E4: Pancolitis (proximal to hepatic flexure)
Severity	S0: Clinical remission S1: Mild UC S2: Moderate UC S3: Severe UC	S0: Never severe S1: Ever severe

*Extent defined by maximal macroscopic inflammation
*Severe defined by Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥ 65

MANAGEMENT

Goals of therapy in children include controlling active symptoms, achieving mucosal healing, optimizing quality of life and minimizing adverse effects of medications, many of which suppress the immune system. The focus in a newly diagnosed patient is to induce remission and thereby improve clinical symptoms. Systemic corticosteroids (CS) have been a mainstay induction therapy for the last 50 years. While CS are effective at quickly improving symptoms, they are associated with a myriad of adverse physical and emotional side effects. Thus, long-term use can be problematic and steroid-sparing strategies are increasingly used in children with IBD. Other therapies used for induction of remission include biologic agents, high dose mesalamine in mild-to-moderate UC and exclusive enteral nutrition (EEN) in small bowel CD.

Biologic Therapy

The use of biologic therapies has transformed management of pediatric IBD over the last 20 years. Infliximab (IFX) and adalimumab (ADA) are monoclonal antibodies against the inflammatory cytokine TNF-α. They are FDA-approved for both induction and maintenance of remission in moderate-to-severe pediatric CD and UC. These medications are superior to thiopurines for achieving mucosal healing (i.e., deep remission), can heal perianal fistulae in CD and improve linear growth in children.[21,22] Several studies have shown that early use of anti-TNF therapy is associated with improvement in clinical outcomes, increased rates of sustained clinical remission, improved rates of mucosal healing

and decreased surgical rates.[22,23] Adverse effects include increased risk of infection related to degree of immunosuppression, infusion reaction (IFX) or reaction at the site of injection (ADA), and hematologic or hepatic toxicity. However, the risk of serious infection with anti-TNF therapy has been shown to be less than in patients with prolonged corticosteroid exposure.[24] Anti-TNF medications were previously associated with increased malignancy risk, though a recent prospective study reported no difference in risk of malignancy associated with exposure to infliximab.[24,25] The pharmacokinetics and pharmacodynamics of these biologic medications differ between children and adults. Children often require higher doses and/or more frequent doses to achieve therapeutic drug levels and maintain a durable treatment response. This can be especially challenging when seeking insurance approval for certain medications and doses.

Several newer biologic agents and small molecules have shown promising results in treatment of IBD but are still not FDA-approved for use in children. These include vedolizumab (α4β7 integrin inhibitor), ustekinumab (anti-interleukin 12/23), rizankinumab (anti-interleukin 23), tofacitinib, upadacitinib (both janus kinase (JAK) inhibitors) and ozanimod (sphingosine-1 phosphate inhibitor).

5-Aminosalicylates and Immunomodulators

Other options for therapy in pediatric IBD include 5-aminosalicylate (5-ASA) medications such as mesalamine and sulfasalazine, immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), antibiotics, and dietary therapy. 5-ASA medications are indicated for treatment of mild-to-moderate ulcerative colitis and can be used as adjunctive therapy in patients with Crohn's disease, though often this drug class is not effective in maintaining remission long term. The PROTECT study demonstrated a minority of study participants with UC achieving corticosteroid-free remission at 52 weeks with mesalamine alone. Milder presentation, higher baseline hemoglobin, and clinical remission at week 4 were factors associated with corticosteroid-free remission at week 52 with mesalamine alone.[26]

Immunomodulators are typically not effective in inducing remission alone but can be used as adjunctive maintenance therapies along with biologics. 6-mercaptopurine (6-MP) is a thiopurine analog that has been shown to maintain corticosteroid-free remission in pediatric IBD.[27] Methotrexate inhibits production of dihydrofolate reductase and can also be effective in maintenance of remission in CD.[28] Both drugs are immunosuppressive and can be associated with hepatotoxicity. Methotrexate is a known teratogen and counselling on safe sexual practices with double contraception is important when using this medication is females of child-bearing age. Prolonged exposure to 6-MP has been associated with an increased risk of lymphoma. Additionally, primary Epstein–Barr virus (EBV) infection in children with IBD receiving 6-MP therapy has been associated with increased risk for severe EBV infections and potential complications like malignancies or hemophagocytic lymphohistiocytosis, and warrants cautious use of 6-MP in EBV naïve patient population.[29,30] T-cell lymphoma is a rare but fatal disease that has been reported in a small number of mostly male patients exposed to both 6-MP and infliximab. Because of this, many practitioners are transitioning to the use of methotrexate rather than 6-MP for concomitant therapy with biologic medications to prevent immunogenicity, especially in males.[28]

Surgery

Surgery remains an integral part of the comprehensive management of children with IBD. Those with moderate-to-severe, treatment-refractory UC may require total colectomy with ileal pouch anal anastomosis (IPAA). IPAA entails resecting diseased colon and constructing a pouch from the distal ileum and anastomosing it to the cuff of rectum to preserve continuity and avoid a permanent ileostomy. Those with CD are at risk for debilitating complications, such as perianal fistulae, abscesses, intestinal strictures, fistulae and perforation. Patients with stricturing CD may require a limited ileocecectomy. Penetrating CD can present with fistulae extending from the bowel to multiple extraluminal locations such as bladder (entero-vesical), vagina (entero-vaginal) and abdominal wall (entero-cutaneous). Many of these complications require surgical intervention and justify aggressive early use of biologic medications, especially in those who present with severe disease phenotypes. Recent population-based data suggest a general decline in surgical rates over time, likely attributed to increased, early use of biologic agents and successful achievement of mucosal healing.

Nutrition

Nutrition is critical to the maintenance and treatment of children with IBD. Specific dietary therapies can be used as primary and adjunctive treatments and are discussed in a separate article.

HEALTH MAINTENANCE

Routine health maintenance visits are integral to the care of children and adolescents with IBD. Assessing growth and pubertal development on a regular basis is important, regardless of disease activity. Some patients with sub-clinical inflammation will still experience poor growth. Thorough physical exam, review of growth charts, routine lab work and trending of the fecal calprotectin (a stool inflammatory marker) are important to routine care. Each patient's immunization status needs to be reviewed at diagnosis. While vaccines should not be delayed in IBD, live virus vaccines need to be avoided in patients treated with immune suppressing

medications such as corticosteroids, immune modulators (such as methotrexate or 6-mercaptopurine) and biologics. Vaccination guidelines are reviewed in a separate article and updated guidelines can be downloaded from the Crohn's and Colitis Foundation website or the Cornerstones Health website. Screening for tuberculosis exposure or latent infection and Hepatitis B immune status need to be obtained prior to initiation of biologic agents.

Longstanding inflammation increases the risk of malignant transformation and cancer, especially in UC. A meta-analysis reported the incidence of colorectal cancer (CRC) among patients with IBD to be 1%, 2%, and 5% after 10, 20, and > 20 years of disease duration, respectively.[31] Significantly higher risk was seen in patients with longer disease duration, extensive disease, and in patients diagnosed at a young age.[32] Surveillance colonoscopy is thus recommended 8-10 years from diagnosis and then every 1-5 years depending on risk factors for neoplasia which include extent and duration of disease, inflammation burden over time and at last colonoscopy, male gender, family history of colorectal cancer under the age of 50, and primary sclerosing cholangitis (PSC) (AGA guidelines). Patients with both IBD and PSC are considered high risk and start surveillance at diagnosis and then annually.

PSYCHOLOGICAL CONSIDERATION

Children with IBD are at higher risk for anxiety and depression.[33] Routine assessment of psychosocial stressors at home and at school should be performed at each visit. Involving a child psychologist early on can help screen for those most at risk while providing coping strategies for adjusting to a chronic illness. Support groups can also provide a valuable resource for patients and families struggling to adjust to a new diagnosis of IBD.

A MULTIDISCIPLINARY TEAM APPROACH

A multidisciplinary care team often includes pediatric GI providers, nurse specialists, social workers, nutritionists, administrative support, clinical research coordinators, and behavioral psychologists. Optimal care involves close collaboration with other clinical specialties including, but not limited to, dermatology, rheumatology, immunology, ophthalmology, pharmacy, psychology, psychiatry, nutrition, radiology, anesthesia and pediatric surgery. Care coordination between outpatient, inpatient and infusion services is integral for patients on biologic medications. A dedicated GI or IBD social worker can serve as a liaison for patients and families serving as a constant, supportive presence. Coordination with schools and colleges is also important to ensure adequate accommodations are available relative to bathroom access and academic support.

TRANSITION OF CARE TO ADULT GASTROENTEROLOGY

Assuring a seamless transition of care for young adults with IBD from pediatric to adult gastroenterology practices is critical and often challenging. Advanced planning and effective communication among the key stakeholders in the patient's care is essential to a successful transition. The timeline is unique for every patient and should be based on a combination of factors including transition readiness, developmental maturity and emotional maturity, which does not always correlate with chronological age. For example, a patient with developmental or cognitive delays may benefit from a later transition to adult GI providers. In general, discussion of transition of care begins in early adolescence as the patient takes a more active role in discussion of their health care needs and management decisions. Once the decision to transition has been completed, a formal sign out between the pediatric and adult gastroenterologist should be completed to ensure adequate communication of salient clinical details. While there is no standard approach, a number of transition models, instruments and checklists are currently available to help support patients through this important phase.

CONCLUSIONS

IBD is a chronic, debilitating condition with rapidly increasing disease burden in the pediatric population worldwide. The presentation of IBD in children and adolescents is variable and primary care clinicians should be familiar with atypical clinical presentations to avoid delays in diagnosis. Treatment focuses on controlling active symptoms and preventing long-term complications with a focus on preserving age-appropriate quality of life. Successful management of children with IBD involves a multidisciplinary team approach. Close attention to emotional health is as important as medical management in this especially vulnerable patient population.

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Authors

Shova Subedi, MD, Warren Alpert Medical School of Brown University; Division of Pediatric Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

Allison L. Behrle Yardley, MD, Warren Alpert Medical School of Brown University; Division of Pediatric Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

Jason M. Shapiro, MD, Warren Alpert Medical School of Brown University; Division of Pediatric Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

Correspondence

Jason M. Shapiro, MD
jshapiro@lifespan.org

Approach to Inflammatory Bowel Disease in Pregnancy

DANA LEY, MD; SUMONA SAHA, MD, MS

INTRODUCTION

Inflammatory bowel disease (IBD) is most commonly diagnosed before or during the peak reproductive years, and for at least 25% of patients, their first pregnancy occurs after diagnosis.[1] Understanding how IBD impacts fertility and pregnancy outcomes as well as how pregnancy impacts the course of IBD is therefore important for the broad range of clinicians involved in the care of these patients.

PRECONCEPTION COUNSELING

Women with IBD of childbearing potential should be queried as part of routine care about their pregnancy plans. Since nearly half of all of pregnancies in the United States are unplanned, it is helpful for healthcare providers to discuss issues regarding pregnancy before the patient reports a positive pregnancy test.[2] Often even a brief conversation held before an unplanned pregnant can help allay fears regarding the safety of IBD medication use during early pregnancy and about being pregnant with IBD.

Women with IBD who desire pregnancy soon should undergo comprehensive pre-conception counseling.[3] General topics to discuss include optimizing diet and nutrition, starting a prenatal vitamin, discontinuing tobacco, alcohol, marijuana and illicit drug use, and getting up to date in vaccinations. It is recommended that women with IBD be up to date on vaccinations for influenza, COVID-19, HPV, and Hepatitis A and B. Depending on their medication usage, they may also need vaccination against pneumococcal pneumonia. Testing for nutritional parameters including vitamin B12, folic acid, vitamin D, iron stores, vitamin B6 and zinc should be considered at this time as well.

Pre-conception counseling should also include education about the importance of conceiving when IBD is in remission and about the safety of IBD medication use during pregnancy, which is a top priority topic for women with IBD who desire pregnancy.[4] Most women can be advised that it is safe continue their IBD medication(s) while they are trying to conceive and during pregnancy.[5] Women on certain medications, namely methotrexate, tofacitinib and upadicitinib, however, should be counseled to discontinue their drug and/or transition to another agent before actively trying to get pregnant. Additionally, women on corticosteroids should be advised to wean off and be in a durable steroid-free remission prior to conception.

Although, in general, fertility is not compromised by having IBD, some women are at higher risk for infertility. Women who have undergone total abdominal colectomy (TAC) with ileal pouch anal anastomosis (IPAA) are a high-risk population for infertility due to the burden of pelvic adhesions causing tubal obstructions as well as the potential for sexual dysfunction caused by decreased lubrication and dyspareunia.[6] These patients as well as others who fail to conceive naturally may benefit from referral to an infertility specialist (**Figure 1**).[7]

Figure 1. Pre-conception Checklist for Patients with IBD

Topics to discuss
Impact of IBD on fertility
Impact of IBD on pregnancy outcomes
Impact of pregnancy on IBD course
Importance of remission at the time of conception
IBD medication safety during pregnancy/discontinuation of teratogenic medications
Initiation of prenatal vitamin and additional folic acid if on sulfasalazine
Items to review
Vaccination history
Habits (i.e., smoking, alcohol use, marijuana use, illicit drug use)
Cancer screening history (e.g., screening for cervical cancer, colon cancer, skin cancer)
Work-up to complete
Check of nutritional parameters
Assessment of IBD activity (e.g., fecal calprotectin, endoscopy, imaging)
Therapeutic drug monitoring labs for biologics
Multi-disciplinary team to assemble
Gastroenterologist
Ob/Gyn
Infertility specialist if applicable
Maternal-fetal medicine specialist
Obstetric medicine specialist

IMPACT OF PREGNANCY ON IBD

Many women fear that pregnancy may cause their IBD to become more active. For some this is a reason for voluntary childlessness.[8] Reassuringly, however, for women with IBD in remission, their course of IBD tends to be the same as in non-pregnant women.[9] During pregnancy and the post-partum period, women with Crohn's disease as well as non-pregnant women with IBD have similar disease courses. However, pregnant women with ulcerative colitis are at increased risk of a disease flare compared to women with Crohn's disease. The reason for this is unclear.[10] About 1/3 of women in remission at the time of conception relapse during pregnancy. These relapses are most common during the first trimester. Conversely, those who achieve remission during pregnancy are likely to remain in remission throughout the rest of their pregnancy.[11] Unfortunately, the majority (about 70%) of women with active disease at the time of conception will have continued or worsened symptoms during pregnancy.[12]

Endoscopic or imaging studies may be required during pregnancy for diagnostic purposes or for assessment of IBD activity. Endoscopy is the most definitive way to monitor and assess disease activity, but given potential risks to the baby and mother, it should be performed if it's necessary for diagnosis or to stage the mother's disease. Flexible sigmoidoscopy is low risk because it can be performed in any trimester without sedation or colonoscopy preparation.[13] Colonoscopy is likely also low risk, but there is a paucity of data. None of the commonly used anesthetics when used in standard doses at any gestational age have been associated with teratogenicity in humans. There is a lack of data on the safety of colonoscopy preparations in pregnant women. If needed, tap water enemas would be safe for use in this population.

Any imaging studies that utilize ionizing radiation (e.g., computed tomography, abdominal x-rays, and small bowel follow-throughs) should be avoided during pregnancy. If there are no alternatives, and imaging is necessary, they can be performed. There are a few options that minimize radiation exposure to the fetus. Ultrasound is the safest imaging modality during pregnancy. It can sometimes be used to evaluate for abscess formation and for location and length of bowel inflammation in centers with expertise.[14] If not possible, magnetic resonance enterography can be used, as it avoids ionizing radiation. It can be done in any trimester, but intravenous gadolinium does cross the placenta. The risk of fetal exposure to gadolinium is unknown.[15]

There are multiple non-invasive methods with which to monitor disease activity in pregnant women with IBD. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are markers of inflammation that reflect disease activity. The ESR must be interpreted carefully during pregnancy as pregnancy can cause increased ESR due to increased levels of fibrinogen. The ESR may increase to 2–3 times the upper limit of normal by the first trimester.[16] CRP levels are usually unchanged to slightly increased during pregnancy.[17] One study showed that median CRP was higher in women with clinically active disease compared to those with inactive disease at both pre-conception and during the first trimester. However, the median CRP was actually lower in women with active disease compared to those with inactive disease during the second and third trimesters.[18] Fecal calprotectin is another useful measure of gastrointestinal mucosal inflammation. It appears that pregnancy itself does not cause an elevation in fecal calprotectin levels in healthy women.[19] It has been demonstrated that higher fecal calprotectin concentration is found in pregnant women with active disease compared to those in remission by physician global assessment or disease clinical scores.[20] A recent study also showed that higher fecal calprotectin in the second trimester was associated with increased incidence of low birth weight, and a higher level in the third trimester was associated with increased incidence of non-elective induction of labor.[21]

If women with IBD develop a flare during pregnancy, in general, a brief course of corticosteroids is considered safe. Initiation of biologic monotherapy would then be appropriate. In general, any medication that is maintaining a patient's disease in remission should be continued throughout pregnancy without being held, as the benefit of maintaining a patient in remission tends to outweigh potential risks of the medication. Would mention not starting a thiopurine (AZA or 6MP) during pregnancy given the risk of pancreatitis and slow onset of action.

IMPACT OF IBD ON PREGNANCY OUTCOMES

Women with IBD face higher risks for certain adverse pregnancy-related and newborn outcomes. These include an increased risk for antenatal hospitalization, venous thromboembolism, protein-calorie malnutrition and blood transfusion.[22] Women with IBD have also been found to be at increased risk for pre-eclampsia, medically indicated preterm delivery, preterm premature rupture of membranes, and delivering infants with low Apgar score.[23] Risk for these adverse outcomes may be mediated by having active disease. A recent systematic review found that in women with active IBD, the pooled ORs for low birth weight [LBW], preterm birth, small for gestational age [SGA], spontaneous abortion and stillbirths were respectively 3.81 (95% confidence interval [CI] 1.81–8.02), 2.42 [95% CI 1.74–3.35], 1.48 [95% CI 1.19–1.85], 1.87 [95% CI 1.17–3.0] and 2.27 [95% CI 1.03–5.04] compared to women with inactive IBD, thus stressing the importance of good disease control during pregnancy.[24]

Given the higher risk for adverse pregnancy and newborn outcomes, the IBD Parenthood Project recommends a multi-disciplinary approach to pregnant women with IBD with early involvement of perinatology and other specialists in obstetric medicine.[3]

MEDICATION SAFETY/DOSING CONSIDERATIONS

The choice of whether to continue IBD treatment during pregnancy should be based on the medication's safety profile, as well as the risk of developing active IBD during pregnancy if the medication were discontinued (**Table 1**). Active IBD has been associated with poor pregnancy outcomes, so in some cases the risk of discontinuing medications may be higher than the risk of the medication itself.

Sulfasalazine and 5-aminosalicylic acid (5-ASA) medications can be safely used during pregnancy. Prior studies have demonstrated that 5-ASA medications are both effective and safe in this population.[25,26] There are similar rates of prematurity, spontaneous abortion, and congenital anomalies in children born to women taking sulfasalazine compared to the general population.[27] Importantly, women taking sulfasalazine should receive folate supplementation, as this medication interferes with metabolism of folic acid and can increase the risk for neural tube defects in the absence of adequate folate levels.[28]

Corticosteroids (including methylprednisolone, prednisone, and budesonide) are also considered low risk during pregnancy. Long-term use of high doses of corticosteroids (e.g., >20 mg of prednisone daily) has been associated with neonatal adrenal insufficiency and requires close monitoring.[29] Corticosteroids may also put women at risk for worsening hypertension during pregnancy, gestational diabetes, as well as preterm delivery due to premature rupture of membranes.[30]

Thiopurines (azathioprine and 6-mercaptopurine) are also thought to be generally safe during pregnancy. One systematic review and meta-analysis showed that thiopurine exposure during pregnancy was associated with preterm birth, but not with either congenital abnormalities or low birth weight.[31] Other studies have shown that discontinuation of thiopurines during pregnancy was associated with higher rates of relapse. Given that active IBD itself has been associated with increased risk for low birth weight, the risks and benefits of thiopurine continuation should be considered.[32,33]

Methotrexate is strictly contraindicated during pregnancy as it is teratogenic. Its use during pregnancy is associated with congenital malformations in 9–17% of exposures.[34] The risk of toxicity is highest at 8–10 weeks' gestation. Women with IBD who are planning conception should discontinue methotrexate and utilize contraception for ideally six months prior to conception.

Women on anti-TNF monotherapy for maintenance are recommended to continue therapy throughout pregnancy according to the Toronto Consensus on Management of IBD in pregnancy.[35] Those who are on combination biologic and thiopurine therapy may be transitioned to monotherapy if they are very low risk (in sustained remission prior to pregnancy and without history of significant medication failures or complications). A large registry, the Pregnancy in IBD and Neonatal Outcomes Registry (PIANO), which included 1490 pregnant patients exposed to immunosuppressive medications, found that the use of biologics, thiopurines, or

Table 1. IBD Medication Safety in Pregnancy and Lactation

Medication/ Medication Category	Considerations for pregnancy	Considerations for lactation
Mesalamine (oral and rectal)	Low risk; safe to continue	Rare cause of diarrhea in breastfed infants
Sulfasalazine	Interferes with folate metabolism which may increase risk for neural tube defects; give with 2 mg of folate daily	Rare cause of diarrhea in breastfed infants
Corticosteroids	Some reports of increased risk of cleft lip and palate with 1st trimester use; monitor for high blood pressure, gestational diabetes; use lowest dose needed to achieve remission	Compatible
Thiopurines (azathioprine and 6-mercaptopurine)	Avoid new starts during pregnancy; Low risk if used as monotherapy; consider discontinuation if used in combination with biologic for antibody protection	Compatible
Methotrexate	Contraindicated due to teratogenicity and also abortifacient; discontinue 3 months prior to conception	Contraindicated
S1P receptor modulator (ozanimod)	Limited human data; discontinue 3 months prior to conception	Contraindicated due to limited data
JAK inhibitors (tofacitinib, upadicitinib)	Limited human data; not recommended for use in pregnancy	Contraindicated due to limited data
Anti-TNF agents (infliximab, adalimumab, certolizumab pegol, golimumab)	Low risk; if patient is in remission consider giving last dose in early 3rd trimester (applies to all drugs other than certolizumab)	Compatible
Integrin antagonists (vedolizumab)	Low risk; if patient is in remission consider giving last dose in early 3rd trimester	Compatible
IL 12/23 receptor antagonists (ustekinumab)	Low risk; if patient is in remission consider giving last dose in early 3rd trimester	Compatible

combination therapy was not associated with increased risk of preterm births, spontaneous abortion, congenital malformations, low birthweights, or infections at one year.[36] Ideally, infliximab in particular should be dosed at a timeframe where the patient receives her next dose soon after delivery.

There is limited data on use of vedolizumab during pregnancy, but typically it is continued throughout pregnancy. Available data suggests that is not associated with increased risk of spontaneous abortion, stillbirth, or congenital anomalies.[37] There is also limited data on the safety of ustekinumab during pregnancy. When used for psoriasis, the safety registries report a 1.7% rate of fetal malformations, similar to that in the general population.[38]

There is even less available data on the use of small molecules during pregnancy. This limited data has found that pregnancy and newborn outcomes including spontaneous abortions, neonatal death, and congenital malformations appear similar in those exposed to tofacitinib and the general population.[39] Data from the ozanimod clinical development program showed no increased fetal abnormalities or adverse pregnancy outcomes in women with ozanimod exposure in early pregnancy.[40] However, it is recommended that pregnancy should be avoided in patients currently taking ozanimod until 3 months after its discontinuation, as clinical experience with it during pregnancy is lacking.

MODE OF DELIVERY

Although women with IBD have a nearly 2-fold higher rate for Cesarean section (C-section) compared to the general population, for the majority of women with IBD the decision to have a C-section can be based on obstetric considerations alone.[41] Two notable exceptions are women with active perianal Crohn's disease (e.g., draining perianal fistula, perianal abscess) and women with IBD who have undergone TAC with IPAA.[42] In these populations, C-section is recommended to avoid trauma to the anus and perineum and avoid future complications such as increased fecal urgency and incontinence.

POST-PARTUM CONSIDERATIONS

Most women with IBD should be encouraged to breastfeed. Only those who are on medications in which breastfeeding is contraindicated or not recommended due to an absence of safety data such as methotrexate or the JAK inhibitors (e.g., tofacitinib, upadacitinib) should be advised not to breastfeed.[43] Women on thiopurines and biologics can be reassured that while these drugs enter breast milk, they are only detectable at very low levels which are not felt to be clinically significant.[44]

Babies born to women with IBD should be vaccinated according to the Advisory Committee on Immunization Practices (ACIP) guidelines.[45] The one notable exception to this is to avoid live virus vaccines in infants less than 6 months of age who were exposed to a biologic other than certolizumab pegol *in utero.* In the United States the only live virus vaccine series recommended for babies under 6 months of age and which should be avoided is rotavirus.

CONCLUSION

Issues regarding fertility, pregnancy, delivery, breastfeeding and newborn vaccination are important to women with IBD. Most patients can be reassured that having a healthy pregnancy is within reach. A multi-disciplinary team which involves primary care, gastroenterology, nutrition, obstetric medicine, maternal-fetal medicine and perinatology may be required to shepherd patients through this vulnerable period and to optimize outcomes.

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Authors

Dana Ley, MD, Gastroenterology Fellow, University of Wisconsin School of Medicine and Public Health.

Sumona Saha, MD, MS, Associate Professor of Medicine, Director of Inflammatory Bowel Disease, University of Wisconsin School of Medicine and Public Health.

Correspondence

Sumona Saha, MD, MS
Medical Foundation Centennial Building
1685 Highland Avenue, Rm 4224
Madison, WI 53705
608-263-1995
ssaha@medicine.wisc.edu

Management of the Hospitalized Patient with Acute Colitis

ABBAS H. RUPAWALA, MD; ERIC MAO, MD; CHARLES BALDI, MD; ADAM KLIPFEL, MD

ABSTRACT

Acute severe ulcerative colitis is a rapidly progressive severe form of colitis that can occur in 20–30% patients with ulcerative colitis. Early recognition, hospitalization at centers with experience and expertise and multidisciplinary treatment is the cornerstone of appropriate management of this condition. After excluding infections and other differentials, patients should be started on parenteral corticosteroids to control inflammation. ASUC patients are at high risk for thromboembolic complications and hence DVT prophylaxis is ideally started as soon as possible in the emergency room and continued throughout hospitalization. Objective criteria should be applied to assess improvement and identify patients who are unlikely to improve without second line/rescue therapy as early as 72 hours on steroid therapy. Infliximab and cyclosporine are the most used options for second line therapy and should be administered under direction by gastroenterologists. Disease progression despite aggressive treatment or non-response to second line therapy, complications such as megacolon, perforation, hemorrhage can occur requiring colectomy as a salvage option in those patients.

KEYWORDS: Acute severe ulcerative colitis, Infliximab, Cyclosporine, Colectomy

INTRODUCTION

Ulcerative colitis (UC) is an immune-mediated disease characterized by chronic inflammation of the colon. It is thought to result from a complex interaction of environmental and immunologic factors with microbiome changes in a genetically susceptible host. Incidence of UC appears to be rising worldwide, attributed in large part to adoption of a Western lifestyle and diet that seems to parallel industrialization.[1] Incidence in the United States appears to have plateaued around 12 per 100,000 person years while the prevalence is estimated to range from 150–211 per 100,000 person years.[2,3] Data from the Ocean State Crohn's and Colitis Area Registry (OSCCAR) for Rhode Island shows higher incidence rates for UC at 15.1 per 100,000 person years.[4]

UC has a relapsing, remitting course and patients may experience episodes of disease flare over their lifetime. Patients classically present with chronic diarrhea, hematochezia, tenesmus, abdominal cramping, weight loss and anemia. Disease extent can vary from limited disease confined to the rectum (proctitis) to more extensive colitis involving the entire colon as described in the Montreal classification and more extensive disease associated with higher risk of colectomy.[5] Disease severity assessed using various criteria can range from mild, moderate to severe. One of the earliest described was the Truelove and Witts criteria which is still used in clinical practice.[6] The Mayo score is another widely used clinical criteria, its major advantage being inclusion of endoscopic appearance for grading disease severity. Most patients have mild-to-moderate and left-sided disease at presentation, but 20–30% patients may present with severe disease at diagnosis or at some point in their lifetime.[7] Some patients may present with severe disease, refractory to outpatient treatment with a rapid course and needing hospitalization referred to as Acute Severe Ulcerative Colitis (ASUC). Historically, patients with ASUC had an in-hospital mortality rate as high as 28% with colectomy being the only salvage option. However, several advances in management over the last 75 years including early disease identification, treatment with corticosteroids, early recognition of steroid-refractory state and development of newer anti-cytokine therapy has dramatically improved outcomes.[8] Despite that about 30% patients with ASUC will need colectomy at three months and mortality rates remain around 1–2%.[9]

DIAGNOSIS

ASUC is often underrecognized, particularly in patients with long standing UC developing a severe flare. Up to 10–15% patients may present with ASUC at initial diagnosis.[7] Using objective criteria may aid early recognition and timely initiation of treatment. Failure to respond to high doses of outpatient steroids (prednisone 60 mg daily), significant anemia or hematochezia requiring transfusion and systemic symptoms are other indicators of aggressive disease. Patients with UC are at high risk of *Clostridioides difficile* infection (CDI) which in turn can trigger a severe disease flare. Furthermore, superadded CDI can increase rate of colectomy in these patients and should be tested and treated if positive in all patients with ASUC.[10] Other enteric infections should be ruled out early in disease course to allow appropriate treatment of colitis. Cytomegalovirus (CMV) infection

can occur particularly in individuals on prior immunosuppressive therapy for their colitis and can also lead to steroid refractoriness. Diagnosis of CMV requires sigmoidoscopy with biopsy to look for inclusion bodies on histopathology and immunohistochemistry may further aid diagnosis. Sigmoidoscopy early in the hospital course (within 24–48 hrs.) may help diagnose certain other conditions such as CDI (although classic pseudomembranes may not be seen in UC with CDI), ischemic colitis, stercoral ulcers, radiation colitis, segmental colitis associated with diverticulosis (SCAD) and provide endoscopic assessment of disease severity and extent to correlate with other markers such as c-reactive protein (CRP) and fecal calprotectin. For all these reasons, gastroenterology team should be consulted early in the hospital course.

Box 1. Best practices checklist for the inpatient with acute severe ulcerative colitis

1. Check for C.difficile in addition to other infections
2. Send quantiferon gold and hepatitis B serology (surface antigen, surface antibody and core antibody total) on admission, preferably before steroids
3. Early gastroenterology consult - Sigmoidoscopy in 24-48 hrs, biopsy for CMV (especially if not responding to steroids or previous biologic agent use)
4. Initiate solumedrol if infectious work up negative – dose no more than 60 mg/day
5. Consult colorectal surgery early, preferably on admission or when considering rescue/salvage therapy
6. Daily monitoring – c-reactive protein, albumin, white count, Xray KUB upright
7. DVT prophylaxis with LMWH or heparin
8. Assess response to steroids by day 3 of solumedrol (Travis index/ Oxford criteria) – consider salvage therapy with infliximab or cyclosporine based on local expertise

MANAGEMENT

Initial management

Patients with ASUC should be hospitalized for close monitoring as the disease can progress rapidly with high risk of complications. Depending on allocation of resources, patients may be best monitored in an intermediate care unit. The goal of initial management is exclusion of other etiologies that can mimic a similar presentation, rapid control of the severe inflammation, prevention of complications and early identification of patients who are likely to need second line therapy.

Treatment of inflammation

The first line agent for treatment of ASUC is intravenous corticosteroids. The usual agents of choice are methylprednisolone typically used at a dose of 60 mg/day or hydrocortisone 100 mg three times daily. Higher doses of methylprednisolone have limited efficacy in terms of therapeutic gain over 60 mg/day with increased risk of side effects.[11] Patients should be closely monitored for improvement in bowel frequency, bleeding and inflammatory markers, particularly CRP. Bowel rest does not improve inflammation and can increase risk of malnutrition and hypoalbuminemia unless patient exhibits severe abdominal pain and peritoneal signs. Antibiotics also have limited efficacy in improving inflammation and should be avoided, particularly due to increased risk of CDI.

Prevention of complications

Patients with ASUC have a 2–3-fold increased risk of deep vein thrombosis (DVT) and should receive prophylaxis with subcutaneous heparin or low molecular weight heparin started immediately in the ER on admission despite having hematochezia.[12] Anti-motility agents such as loperamide can precipitate mega-colon and should also be avoided. Additionally, non-steroidal anti-inflammatory medications can worsen inflammation and should be avoided. In addition to routine labs and inflammatory markers, daily abdominal flat plate X-rays may help monitor for megacolon. These patients may also develop perforation without classic features of acute abdomen while on high dose steroids or other immunosuppressive therapy. In preparation for possible treatment with an anti-TNF, tuberculosis testing with QuantiFERON gold and assessment for hepatitis B infection is standard of care and important to do early and not delay initiation of rescue therapy if needed. Colorectal surgery consultation should be obtained early in hospital stay to allow patients to understand surgical options in case of disease progression on medical therapy.

Second line (Rescue) therapy

As many as a third of patients are unlikely to respond to steroids alone during their hospital stay and may need initiation of second line/rescue therapy failing which they remain at high risk of requiring colectomy.[13] Presence of deep ulcers on early sigmoidoscopy and failure of outpatient oral steroids may be early indicators of need for second line/rescue therapy. Response to steroids should be judged as early as day 3 using Oxford criteria (stool frequency > 8 bowel movements or CRP > 45 on day 3 of hospital stay predicting an 85% likelihood of colectomy during that admission).[14] Other predictive indices can also aid identification of patients needing escalation to second line or rescue therapy. However, the key is to identify this early and not leave patients on high dose parenteral steroids for longer than 5–7 days due to lack of further benefit and increased risk of complications. The two most commonly utilized medical rescue therapies for corticosteroid-refractory ASUC patients are infliximab (IFX) and cyclosporine (CsA).

CsA is a rapidly acting calcineurin inhibitor with high

rates (65–80%) of short-term clinical response.[15,16] Calcineurin inhibitors have a narrow therapeutic window and are associated with nephrotoxicity, neurotoxicity (seizures or tremor), electrolyte abnormalities (magnesium, potassium), hypertension, and opportunistic/serious infections. Contraindications include hypocholesterolemia (total cholesterol < 80) and renal insufficiency. Given potential toxicities, CsA is implemented as induction therapy and subsequently as bridging therapy to another long-term maintenance medication. In randomized controlled trials with steroid-refractory ASUC patients, CsA demonstrated greater clinical response rates than placebo with a trend towards lower risk of colectomy but there were no differences in response or colectomy rates between doses of 2mg/kg/day and 4mg/kg/day.[15,16] CsA is started at a continuous infusion rate of 2mg/kg/day with a target concentration of 150–250 ng/mL. If the patient responds within 7 days, they can be transitioned to oral CsA and then subsequently bridged to maintenance therapy such as thiopurine or vedolizumab. Before starting CsA, creatinine, cholesterol, and magnesium need to be evaluated. While on therapy, cyclosporine levels, electrolytes, cholesterol, creatinine, and blood pressure are monitored daily. Given the intricacies of monitoring CsA therapy, local expertise is crucial.

Another less commonly utilized calcineurin inhibitor for medical rescue therapy is oral tacrolimus. Randomized controlled trials on steroid-refractory ASUC showed higher rates of clinical response (50%) and mucosal healing (44%) in the tacrolimus group compared with placebo after 2 weeks of therapy.[17] The target trough drug level for tacrolimus is 10 to 15 ng/ml.[18] The lack of patients requiring colectomies in the tacrolimus trials suggests different patient populations than other trials of corticosteroid-refractory ASUC patients; there remains uncertainty in the ability of tacrolimus to decrease risk of colectomy.[19]

Another crucial aspect of calcineurin inhibitor rescue therapy in ASUC is that it is a bridge to another therapy. Traditionally, calcineurin inhibitors were a bridge to immunomodulator therapy. However, current practice has expanded to include destination therapy in infliximab and vedolizumab. In patients who received calcineurin inhibitor as induction therapy with vedolizumab as maintenance therapy, at 12 months, 68% experienced colectomy-free survival.[20] The role of newer small molecule JAK inhibitors or S1P inhibitors as destination therapy after cyclosporine remains to be determined. A key consideration in these patients is the need for pneumocystis jiroveci pneumonia prophylaxis with trimethoprim/sulfamethoxazole when patients are on three or more immunosuppressive agents.

IFX is a monoclonal antibody that is widely used to treat moderate to severe ulcerative colitis. It has been well-established as second-line medical rescue therapy in ASUC patients. However, an optimal dosing strategy is not well established. The induction strategy for outpatient moderate-severe ulcerative colitis (5 mg/kg at weeks 0, 2, and 6) can be adopted in the acute setting of a hospitalized ASUC patient but a better understanding of infliximab pharmacokinetics suggests that intensive IFX dosing may be required. ASUC is associated with fecal wasting of IFX and accelerated infliximab clearance through intestinal protein loss leading to hypoalbuminemia.[21,22] Intensive IFX dosing refers to a shortened interval between infliximab doses (dose stacking) and/or administering a higher dose than 5 mg/kg. There were no clinical trials comparing infliximab dosing regimens but meta-analyses of observational studies demonstrated no difference in short-term risk of colectomy between intensive and standard dosing. However, studies demonstrated that a lower colectomy risk (RR, 0.24; 95% CI 0.08-0.68) was achieved with a higher IFX induction dose (10mg/kg) compared with dose stacking with standard IFX dose (5mg/kg).[23-26] Ongoing prospective studies will provide additional insight on this question but intensive IFX dosing, particularly high dose induction (10 mg/kg), should be considered in ASUC patients at greatest risk for accelerated drug clearance.

The decision to utilize CsA or IFX as rescue therapy in steroid-refractory ASUC depends on prior biologic exposure, patient preference, and local provider expertise. Advantages of CsA include rapid onset of action, pharmacokinetics are not adversely affected by hypoalbuminemia. Advantages of IFX include a relatively better safety profile and the ability to continue IFX as maintenance therapy. Two open-label RCTs demonstrated no significant difference in efficacy to avoid colectomy between IFX and CsA regimens on short-term and long-term follow-up.[27-29] However on meta-analysis of observational cohorts, lower 3-month and 12-month risks of colectomy were seen in patients treated with infliximab.[13] Another consideration is the safety and efficacy of a third-line medical rescue therapy (sequential therapy). A systematic review of sequential therapy revealed short term response rates of 62.4%, colectomy rates at 3 months of 28.3%, serious infections in 6.7%, and death in 1%.[30] Overall, studies suggest that IFX and CsA are comparable in terms of efficacy however providers should be cognizant of potential side-effects of CsA as well as the risks of sequential therapy.

Finally, the introduction of new small molecule agents with rapid onset of action has led to interest in a potential role for novel ASUC therapy. Tofacitinib is a small-molecule that inhibits JAK which is vital to pro-inflammatory cytokine cascades. A retrospective case-control study on biologic-experienced ASUC patients who received tofacitinib in addition to IV corticosteroids showed that a higher dose of 10mg three times daily for 3 days was associated with lower 90- day colectomy risk and similar rates of complications when compared with controls.[31] While these results are encouraging, this strategy needs to be further studied in prospective studies before routine implementation.

ROLE OF SURGERY

The management of ulcerative colitis (UC) has changed dramatically over the last two decades as medical management has made massive strides forward with availability of multiple biologic agents and small molecules. Patients requiring surgery generally fall into one of the following categories: patients with colonic neoplasia, those experiencing significant adverse effects of medications or more commonly, those with severe disease refractory to medical management.[32] Patients failing medical management may be those that have failed multiple treatment attempts and present for elective surgery, or those hospitalized with severe or fulminant disease that may require more urgent or emergent intervention.

ASUC is ideally managed non-operatively, as the risk of surgical complication is high and the preferred operation for ulcerative colitis, restorative proctocolectomy with J-pouch, is not possible in the acute state. Colorectal surgery should be consulted early in the hospital course given the rapidity of disease progression. Medically refractory disease, typically defined as nonresponse to appropriately dosed IFX or CsA, is often main indication to proceed with surgery. In this regard, the amount of time varies widely from center-to-center, but many allow for at least three full days after initiation of salvage therapy with IFX or CsA to assess for improvement before performing surgery. That said, there are no firm guidelines in patients with smoldering disease and different management strategies are employed at various institutions. Certainly, patients with ASUC who develop any life-threatening complications such as colonic perforation, toxic megacolon and severe hematochezia may need more emergent surgery. Toxic megacolon is characterized by sloughing of the mucosa and sepsis occurs due to loss of the mucosal barrier integrity. Patients present with fever, tachycardia, leukocytosis, and often with colonic ileus and distension that is readily apparent on plain film. Patients with toxic megacolon are likely to progress to septic shock and death without source control in the form of total colectomy with ileostomy.[32] Although a rare complication, colonic perforation due to acute severe ulcerative colitis may occur. When it does, emergent colectomy is required. Additionally, a small percentage of patients may experience massive colorectal hemorrhage necessitating immediate intervention.

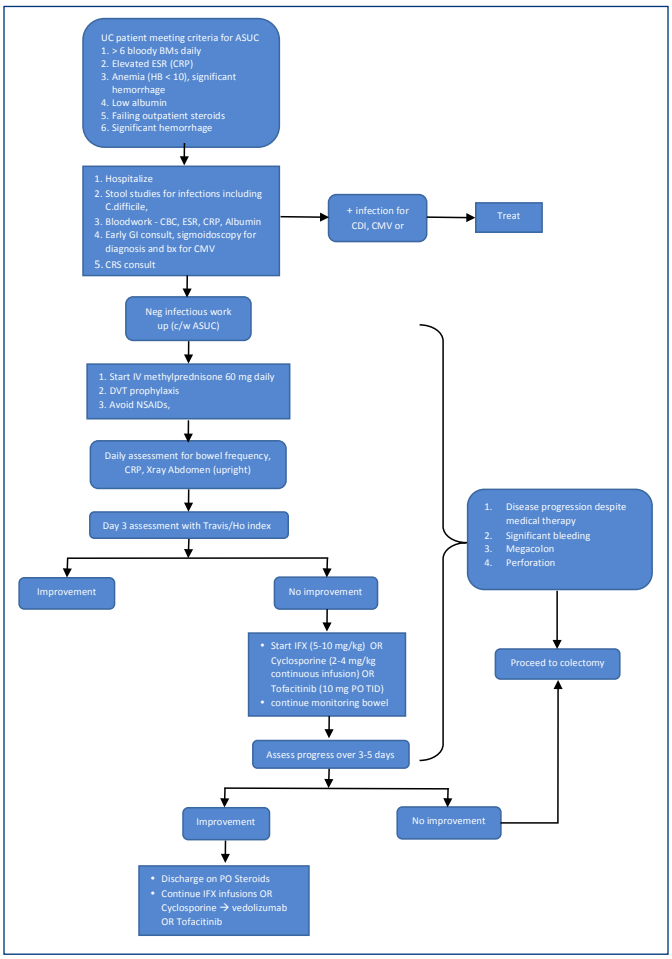
The decision to proceed with surgery is not always as clear as in these emergent situations. Patients failing medical management not having an absolute indication for surgery (perforation, megacolon) will typically benefit from surgery for symptom control. The goal from a surgical standpoint is to operate before any perforation occurs, or before the patient becomes so debilitated that the surgery results in complications, prolonged hospitalization and possible death. Time is of the essence with higher risk of in-hospital mortality for those undergoing surgery after a week of admission.[33] Effective communication and collaboration between gastroenterologist, colorectal surgeon, and the primary team is extremely important in forming a multidisciplinary and individualized approach for each patient.[34] Hence, involving the colorectal surgery early (when considering salvage/rescue therapy) gives the patient and family time to become familiar with the option of surgery and rather than waiting until surgery is imminent or emergent. Surgery should not be presented as a last resort but an important option that may be the best option for some situations. Consideration should also be given to transferring patient to a tertiary care center with expertise in colorectal surgery as the experience and volume of colorectal surgeons can impact outcomes including mortality in ASUC.[33]

The long-term surgical management for patients with UC is total proctocolectomy and creation of an ileal pouch anal anastomosis (IPAA). This is typically achieved in three stages. The first stage in ASUC is colectomy and end ileostomy with the rectum left in situ. If there is concern for the viability of the rectal stump, or concern for breakdown of the staple line, then the end of the stump can be brought up into the inferior portion of the wound as a mucous fistula. In the acute setting, reconstruction is generally not indicated. In select cases, if the patient is not too de-conditioned, and thought to be a suitable surgical candidate and is agreeable, reconstructive surgery can be offered. Approximately 6 months after initial surgery, once the patient recovers, in the second stage removal of the rectum with Ileal J-pouch and anal anastomosis, often with a temporary loop ileostomy is standard of care. The third stage is performed about 2–3 months later where the loop ileostomy is reversed to allow patient to have a continent fecal stream. The timing of IPAA creation may be delayed in women of childbearing age considering its impact on fertility.

CONCLUSION

ASUC is a medical emergency and timely recognition and treatment can have a huge impact on patient outcomes. Patients may be best cared for at centers with experience in dealing with this condition with expertise in gastroenterology and colorectal surgery. Standardized protocols may help further streamline their care (**Figure 1**). Corticosteroids play a vital role in initial control of inflammation with second line rescue agents offering a chance at avoiding colectomy. The positioning of newer, small molecule-based treatments (JAK inhibitors) in the management of ASUC is yet to be determined. Despite these advances, a significant number of patients will still need colectomy and close collaboration with surgery is vital in the successful implementation of any treatment protocols.

Figure 1.



ASUC – Acute severe ulcerative colitis, BM – bowel movement, CBC – complete blood count, CDI – Clostridioides difficile infection, CMV – cytomegalovirus, CRP – c-reactive protein, CRS – Colorectal surgery, IFX – infliximab, DVT – deep vein thrombosis, ESR – Erythrocyte sedimentation rate, NSAIDs – Non steroidal anti-inflammatory drugs, UC – Ulcerative colitis

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Authors

Abbas H. Rupawala, MD, Department of Medicine, Division of Gastroenterology, UMass Memorial Medical Center, UMass Chan Medical School, Worcester, MA.

Eric Mao, MD, Department of Medicine, Division of Gastroenterology, University of California Davis Health, Sacramento, CA.

Charles Baldi, MD, Department of Surgery, Rhode Island Hospital, Providence, RI.

Adam Klipfel, MD, Division of Colorectal Surgery, Brown Surgery/ Brown Physician's Inc., Providence, RI.

Correspondence

Abbas H. Rupawala, MD
abbas.rupawala@umassmed.edu

Surgical Management of Inflammatory Bowel Disease

VINCENT P. ANTO, MD; AARON J. DAWES, MD, PhD; MATTHEW VREES, MD; ANDREW R. WATSON, MD; AMY L. LIGHTNER, MD

INTRODUCTION

Inflammatory bowel disease (IBD) is a spectrum of inflammatory conditions, including ulcerative colitis (UC) and Crohn's disease (CD). Although IBD primarily affects the intestinal tract, extraintestinal manifestations, such as musculoskeletal, ophthalmologic, and cutaneous conditions, are common. Over 1.6 million Americans carry a diagnosis of IBD and worldwide prevalence rates continue to rise over time.[1] Despite major advances in medical management, surgery continues to play a supportive and complementary role in the treatment of IBD.[2,3] Between 20–40% of UC patients and up to 75% of CD patients will require surgery in their lifetime, with most operations taking place due to either failure of medical management or disease complications, such as fulminant colitis, intestinal obstruction, infection/fistula, or neoplasia.[3] This review will focus on several advances in management of IBD from the surgical perspective.

TRENDS, INDICATIONS, AND TIMING OF SURGERY IN THE BIOLOGIC ERA

Whether or not surgery for IBD has become less common as medical management improves remains complex and somewhat unclear. Several large cohort studies appear to demonstrate a reduction in colectomy rates among UC patients over time that coincides with an increased use of immunomodulatory and biologic medications.[4-6] Among hospitalized patients with severe UC, infliximab has been associated with a significant reduction in the risk of colectomy in multiple randomized trials.[7,8] However, several population-based studies have found both no difference in the long-term risk of colectomy and no change in emergency colectomy rates over time, suggesting that biologics may be more useful in shifting urgent procedures to elective setting rather than obviating the need for surgery altogether.[9-11] Interestingly, one large institutional sample and several nationwide cohort studies have demonstrated an increase in the proportion of colectomies performed for either dysplasia or cancer, again suggesting that medical management may lead to better short-term but not necessarily longer-term disease control.[12-14]

Rates of surgical resection among patients with CD also appear to be decreasing over time and in conjunction with an increased use of biologic medications.[9,15] Several authors note, however, that changes in surgery rates also parallel changes in other potential confounding factors, such as disease severity at diagnosis and cigarette smoking, making causal links less certain. At least one nationwide cohort study also found that, while primary resection rates dropped by nearly two-thirds, secondary resection rates remained unchanged, suggesting that some patients either remain refractory to medical therapy or experience decreasing efficacy over time.[15] Although multiple clinical trials have demonstrated an association between biologics and lower rates of anal fistula surgery, similar trends have not necessarily been reproduced in population-based studies.[9,16-19]

The impact of biologics on surgical complication rates also remains hotly debated. Multiple retrospective single institution studies have demonstrated mixed results, leading to confusion and conflicting recommendations.[20-22] Recent results from the PUCCINI trial, however, finally provide some clarity, at least for anti-TNF medications. Based on a prospective cohort of patients undergoing abdominal surgery for either UC or CD at 17 United States (US) centers, Cohen et al report no difference in either overall infection or surgical site infections rates between patients with recent a exposure to anti-TNF agents (within 12 weeks of surgery) and controls.[23, 24] Moreover, patients with detectable anti-TNF levels appeared to have no increase in either overall or surgical site infection rates when compared to controls, calling into question prior theories regarding dose response rates. Armed with these results, many surgeons now choose to continue anti-TNF medications during the preoperative period or to time surgery based upon the medication's dosing interval. The peri-operative safety of newer biologic and small molecule therapies are still under investigation, although multiple studies on vedolizumab appear to show no clear increase in complication rates.[25,26] Optimal timing for restarting patients on therapy after surgery and the associated prophylactic benefit of various therapies is less well established; most surgeons choose to restart biologic medications at 4 to 8 weeks after resection, depending on recovery and functional status.[27,28]

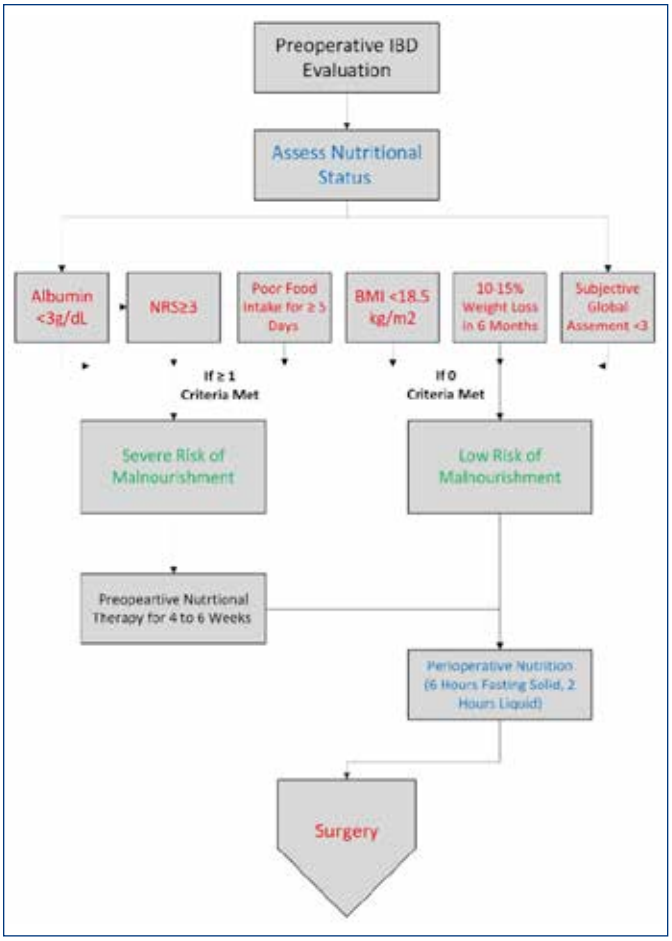
ENHANCED RECOVERY PROTOCOLS

Enhanced recovery after surgery (ERAS) protocols have been a paradigm shift in perioperative management. Born out of

the general colorectal field, ERAS protocols aim to promote faster recovery after surgery.[29] The encompassing approach focuses on preoperative counseling, nutrition optimization, standardized anesthetic regimens, multimodal pain control, and early initiation of mobilization and enteral nutrition.[30] As evidence has demonstrated improved outcomes in colorectal procedures, such protocols are being adopted in IBD patients.

The prehabilitation phase for scheduled procedures in IBD patients focuses on nutritional status and supplementation.[31, 32] The chronic inflammatory and malabsorptive state associated with IBD produces a high risk for malnutrition. Malnourished patients are at significantly higher risk for complications following surgical procedures.[33,34] In elective procedures, guidelines recommend thorough assessment of nutritional status.[31,32] For patients identified as being malnourished, surgery should be delayed, and nutritional therapy initiated.[31,32] Enteral therapy is generally preferred to parenteral nutrition unless contraindications exist.[35] (**See Figure 1**.)

Figure 1. Perioperative nutritional assessment and optimization in IBD patients.



(Adapted from da Silva et al. 2021 and European Society for Clinical Nutrition and Metabolism guidelines.31,36)

Patients in the ERAS protocol can have clear liquids up to 2 hours prior to anesthesia. Intravenous fluids are limited. Epidural analgesia is used, and premedication is withheld. Standardized multimodal pain regimens and anesthesia are used in the perioperative setting. Decompressive gastrointestinal tubes are not routinely placed, and oral intake is initiated as soon as patients recover from anesthesia. Patients are advanced to solid food as tolerated. Urinary catheters are removed on post-operative day one and early ambulation is encouraged.[29, 30] Outcomes from ERAS protocol in ileocecectomies for CD have demonstrated shorter return of bowel function, initiation of solid oral intake, and earlier discharge from the hospital.[37, 38]

MINIMALLY INVASIVE SURGERY

Minimally invasive surgery has revolutionized intraabdominal procedures. The advantages of laparoscopic procedures in IBD has been supported in the past two decades of literature. In general, laparoscopic interventions are associated with decreased pain, ileus, and hospital stays when compared to open operations.[39,40] Laparoscopic procedures have lower overall costs then open procedures in the IBD population.[39] Minimally invasive operations produce fewer adhesions compared to open surgeries, which has increased importance for CD patients given the chronic nature of the disease and requirement for multiple operations.[41]

While it has been well established that the use of laparoscopy has resulted in shorter length of stay postoperatively, improved body image, decreased infertility rates, and decreased intravenous narcotic use among IBD patients, in recent years, the da Vinci robot (Intuitive Surgical, Sunnyvale, California) has become an increasingly popular and accepted modality in colorectal surgery for both benign and malignant conditions.[42-48] Many studies including meta-analyses have now reported equivalent safety and efficacy with a robotic approach in colorectal operations as compared to conventional laparoscopy.[49] The improved dexterity, visualization and ergonomics of the robotic platform have contributed to the surge in the adoption of the robotic platform. This trend of increased use has been seen in IBD surgery with many IPAAs in UC and segmental resections in CD now being performed on a robotic platform despite an increased cost and lack of haptic feedback.[50-52]

The most common operation performed in Crohn's disease is an ileocecal resection. A robotic approach allows the surgeon to perform an intracorporeal anastomosis (ICA), which has been associated with decreased rates of postoperative ileus and decreased incisional hernia rates since the extraction site can be moved off the midline.[53-57] An ICA also minimizes the amount of colon mobilization necessary, which allows the duodenum to remain in the retroperitoneum protected by the right colon and its mesentery. This is relevant in CD since most fistula to the duodenum in

CD originate from recurrent ileal disease after an ileocolic resection. These can be quite difficult to treat. Thus, by avoiding mobilization of the ascending colon, rates of fistula to the duodenum may be decreased.[58]

While there are a limited number of published series of a robotic approach in CD, there are many more for UC given the most common operation involved a pelvic dissection, proctectomy, with IPAA. Several series have shown a robotic approach is safe with equivalent short-term postoperative outcomes to a laparoscopic approach.[59-61] A case-matched comparison of robotic versus laparoscopic proctectomy showed no difference in postoperative complications, and a trend toward improvement in conversion rate, time to bowel function, and LOS with the robotic approach.[62] An observational series including 81 robotic versus 170 open IPAA from a single institution described similar short-term outcomes with improved LOS in the robotic group, but longer operative times and higher readmission rates.[63]

Transanal total mesorectal excision (TaTME) refers to a retrograde laparoscopic approach combined with a transabdominal laparoscopic approach to remove the rectum. This technique was initially described and mainly utilized in the treatment of low rectal cancers.[64] It has the advantage of improved visualization of the natural planes in the pelvis, especially in the narrow male pelvis. This approach to proctectomy has been embraced by highly trained and skilled surgeons, but some recent reports of CO_2 embolism with this technique have led to concerns with this approach.[65] There have been individual case reports of laparoscopic total abdominal colectomy with TaTme and ileal anal pouch for ulcerative colitis.[66] Although these case reports are intriguing, much more data needs to be collected before this becomes a recommended approach to this complex disease and should be considered experimental at this time.

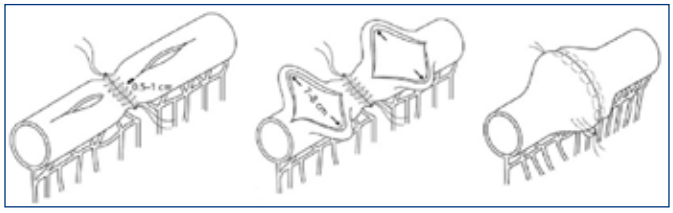
While data on robotic surgery for CD and UC continues to evolve, the current studies that a minimally invasive approach to IBD offers benefits to the patient. The robotic platform presents improved visualization, instrumentation, and dexterity.

ANASTOMOTIC CONFIGURATIONS

A critical component of bowel resections is the ensuing anastomosis. In CD this new connection is commonly the site of early disease recurrence.[2] Recurrence at the anastomosis can be as high as 35–85% when evaluated endoscopically, and recurrence requiring surgery can be up to 50% within 20 years.[3,67,68] Surgical techniques to reduce anastomotic disease recurrence and associated complications continue to be evaluated. In the general population, surgical staplers have demonstrated comparable outcomes to hand-sewn anastomoses, with some studies demonstrating lower leak rates after ileocolic resections.[69] Side-to-side anastomosis (STSA) are commonly performed using a stapled technique. In the setting of IBD, particularly in CD, the STSA may create a non-peristaltic reservoir that promotes early disease recurrence.[70] End-to-end anastomosis (ETEA) produces a more physiologic connection. Studies have demonstrated similar recurrence rates when comparing ETEA to STSA, but ETEA may produce improved quality of life, easier endoscopic evaluation, and less health care utilization.[70]

The Kono-S anastomosis was initially created by Dr. Toro Kono and colleagues in Japan in 2003 in an effort to reduce anastomotic recurrence.[71] The basis of the technique is an antimesenteric functional end-to-end anastomosis. The anastomosis has produced promising results with surgical recurrence-free survival rates of 98.6% over a 10-year period.[72,73] Theoretical benefits of the anastomosis include a supporting column to maintain diameter limiting stenosis.[72] It is a functional ETEA which allows for easier endoscopic monitoring and interventions if stenosis does occur.[72,73] **(See Figure 2.)**

Figure 2. Schematic diagram of the Kono-S anastomosis



(Adapted from Luglio and Kono 2021.74 Licensed by Creative Commons https://creativecommons.org/licenses/by-nc/4.0/)

MESENTERIC RESECTION IN CROHN'S SURGERY

A significant volume of research has been conducted to determine how to prevent postoperative recurrence of CD following an ileocolic resection. Some studies have focused on the timing of resuming postoperative medical therapy. Others have looked at surgical techniques at the time of ileocolic resection including anatomic configuration of the anastomosis and performing a stapled versus handsewn anastomosis. Interestingly, there is recent evidence to suggest that CD may be a disease of the mesentery rather than just the mucosa of the bowel alone. In CD, the transmural inflammation facilitates increased bacterial translocation into the creeping fat. These translocating antigens and activate adipocytes which are cells than have complex metabolic and immunologic functions.[75] Additionally, it is thought that functional abnormalities in the mesenteric structures exert an inflammatory effect: the secretion of adipokines that have endocrine functions contribute to immunomodulation through a response to afferent signals, neuropeptides, and functional cytokines; mesenteric nerves are involved in the pathogenesis through neuropeptides; and lymphatics in the mesentery may obstruct, remodel, and impair contraction,

contributing to the irregularly thickened mesentery seen in CD. Interestingly, the interaction between neuropeptides, adipokines, and vascular and lymphatic endothelia leads to adipose tissue remodeling. This makes the mesentery an active participant in CD, seemingly as much as the bowel itself.[76] However, the mesentery is typically spared, or left *in situ*, during resection for CD, unlike resections for adenocarcinoma of the colon where a high ligation is performed.

Findings from a retrospective review by Coffey et al spearheaded momentum to consider performing a high ligation in CD at the time of an ileocecal resection.[77] In this study, those patients who underwent a high ligation (n=34) compared to those with a mesenteric sparing approach (n=30) had a significantly lower rate of surgical recurrence (40% vs 2.9%; p=0.003). The mesenteric disease activity in this study predicted surgical recurrence, underscoring the relevance of the mesentery in driving disease recurrence.[77] This has prompted the initiation of several international multicenter randomized control trials to study this particular question of whether a high ligation at the time of ileocecal resection can reduce rates of disease recurrence following an ileocecal resection.

SEGMENTAL COLECTOMY IN CD

Although medically refractory Crohn's colitis has traditionally been treated with either subtotal colectomy (STC) or total proctocolectomy (TPC), there is growing interest in performing more limited resections, at least for select patients. Compared to STC or TPC, segmental colectomy (SC) allows for preservation of bowel length and function as well as, potentially, a lower likelihood of stoma formation. On the other hand, these benefits must be weighed against the risk and timing of disease recurrence as well as the possibility of higher rates of surgical complications, including anastomotic leak.

Multiple observational studies have compared SC to STC, including two systematic reviews. Tekkis et al (2006) found no difference in overall or surgical recurrence, although patients undergoing SC required reoperation an average of 4.4 years earlier than those undergoing STC.[78] Angriman et al (2017) performed an updated review, including a total of 11 studies and 1436 patients.[79] Again, there was no difference in overall or surgical recurrence between the groups even when limiting the analysis to studies performed during the biologic era. Interestingly, however, patients undergoing SC had a significantly lower rate of any stoma (OR 0.26, p=0.001) and permanent stoma formation (OR 0.52, p=0.001).[79] Overall, recurrence rates appear to vary between 40–60% depending on the population and follow-up period.[80-83]

Although neither review specifically commented on anastomotic leak, Kiran et al (2011) found no difference in anastomotic leak (2% vs. 3%, p=1.0), abdominal abscess (4% vs. 2%, p=0.59), or 30-day readmissions rates (16% vs. 7%, p=0.13) in a large, retrospective series of patients undergoing either SC or STC for Crohn colitis.[84] Angriman and colleagues did find a higher rate of post-operative complications among patients undergoing SC when compared to STC; however, they provided no additional information regarding the type or severity of the complications they identified.[79]

As with many decisions in IBD, the choice between SC and STC in the setting of Crohn's colitis should be individualized. Surgeons need to weigh the risks and benefits of surgery, including how well a patient would tolerate a major complication and how likely a patient will be to adhere to ongoing surveillance. After safety concerns are met, quality of life becomes paramount. SC offers better bowel function, on average, than STC or TPC without an apparent difference in the likelihood of recurrence. For that reason, select patients with segmental inflammation that either does not respond to medical management or results in a local complication (e.g., fistula or stricture) are increasingly being offered SC and continued surveillance rather than STC or TPC.

SURGICAL CONSIDERATIONS FOR DYSPLASIA

Dysplasia of the colonic mucosa remains a controversial topic. There are two major classifications of this disease process associated with ulcerative colitis. The first is the histologic presence of dysplasia obtained by random biopsies at the time of surveillance colonoscopy, referred to as invisible dysplasia. The other is visible dysplasia best described using the Paris Classification combined with Kudo pit pattern. Both pathologic classifications have gone through significant evolution over the past 20 years and have resulted in changes in recommendations of treatment.

Visible lesions were (previously sometimes referred to as DALMs) considered aggressive and the presence warranted a total proctocolectomy. The term DALM (Dysplasia Associated Lesion or Mass) is no longer used and instead, lesions should be described according to the Paris Classification. Recent studies support colon preservation if the lesion can be endoscopically removed in its entirety and without evidence of malignancy.[85] Some lesions require advanced endoscopic skills for proper removal and endoscopists should appropriately refer to a colleague with those skills for endoscopic mucosal resection (EMR) or endoscopic submucosal dissection; in that setting, the best approach is to leave the lesion alone but mark near it (4–5 cm distal) with India Spot. Manipulation of the lesion with even biopsy can result in scarring that makes complete endoscopic removal technically more difficult. Long-term outcomes demonstrate that 50–65% of patients will develop metachronous adenomas similar to rates seen in non-UC adenoma cohorts. With close endoscopic surveillance many of these patients can avoid colectomy without a significant risk of malignancy.[86]

The finding of invisible dysplasia has been considered a predictor of developing a future malignancy and the

presence of co-existent cancer. The nomenclature has been simplified to indefinite for dysplasia (IND), low-grade dysplasia (LGD) and high-grade dysplasia (HGD) with noted significant interobserver variability.[87] Patients with HGD, defined as severe nuclear changes and the nuclei extending to the upper third of the cell, should undergo total proctocolectomy. The decision of colectomy vs. continued surveillance in patients with LGD, defined as cells having enlarged hyperchromatic nuclei limited to the lower two thirds of the cell, is still controversial. Historically, most surgeons and gastroenterologists agreed that surveillance in these patients is acceptable with low risk of malignancy. However, some recent studies advocate for colectomy in these patients due to 9–20% of patients progressing to carcinoma in an average of 6 years.[88]

PERIANAL FISTULIZING DISEASE

Perianal fistulas are a major source of morbidity in Crohn's disease with 17–50% of patients experiencing fistula during the duration of their disease.[89] Rates of fistula closure have improved with the use of biologic medical therapies.[18,19] Newer surgical techniques for complex fistula, such as ligation of the intersphincteric fistula tract (LIFT), have aimed to improve healing while preserving fecal continence.[90] Rates of healing after the LIFT procedure have been shown to be 40–60% with low rates of sphincter compromise.[90,91] In addition to intrabdominal surgery, minimally invasive methods have been developed for fistula procedures. Video-assisted anal fistula treatment (VAAFT) is a sphincter sparing technique with improved visualization of the internal opening of the fistula tract.[92] In addition to sphincter sparing, advantages of this novel method include faster healing and earlier return to work when compared to traditional seton techniques.[93] Given high recurrence rates and surgical morbidity, there has been an interest in augmented healing of fistula with various products such as plugs, glues, and other biomaterials. Adipose derived mesenchymal stem cells (ADSC) have shown promise in a phase III randomized control trial where healing rates were 50% versus 34% in the placebo arm.[94] There has yet to be a definitive approach to management of challenging fistula in the setting of CD. The vast array of techniques and therapeutic adjuncts allow the surgeon to tailor the approach to the individual patient.

TELEMEDICINE IN THE SURGICAL PATIENT

Telemedicine and its rapid evolution have much to offer IBD surgery; it will play an increasing role in IBD surgical care. Telemedicine has been present in healthcare since 2000 and rapidly expanded with advances in telecommunication capabilities. The COVID pandemic transformed the landscape for telemedicine and rapidly advanced physician and patient awareness and acceptance.[95] Currently, 15–20% of outpatient visits are conducted using telemedicine at a national level.

Due to the complexity of IBD patients, their care is typically conducted in a multi-disciplinary approach including several non-surgical teams. Telemedicine enables these teams to coordinate care and come together using video conferencing.[96] Telemedicine fundamentally enables patients and physicians to access patients at a distance. This has implications for diversity, equity, and inclusion for the IBD care of all patients.

CONCLUSION

The ever-changing landscape of IBD treatment presents a unique balance of medical and surgical co-management. IBD practitioners must be well versed in advances in the entire field of these inflammatory conditions to provide optimal patient care. A multidisciplinary approach involving the surgeon, gastroenterologist, pathologist, radiologist, nutritionist, and others with patient engagement is critical to optimal patient management and outcomes.

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(References 50–96, ...)

Authors

Vincent P. Anto, MD, University of Pittsburgh Medical Center.

Aaron J. Dawes, MD, PhD, Stanford University School of Medicine.

Matthew Vrees, MD, Warren Alpert Medical School of Brown University.

Andrew R. Watson, MD, University of Pittsburgh Medical Center.

Amy L. Lightner, MD, Cleveland Clinic.

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Correspondence

Vincent P. Anto, MD

antovp@upmc.edu

Nutritional Management of Inflammatory Bowel Disease

RAHIYA REHMAN, MD; BETH PINKOS, MS, RDN; JASON M. SHAPIRO, MD; CAROLINA CEREZO, MD

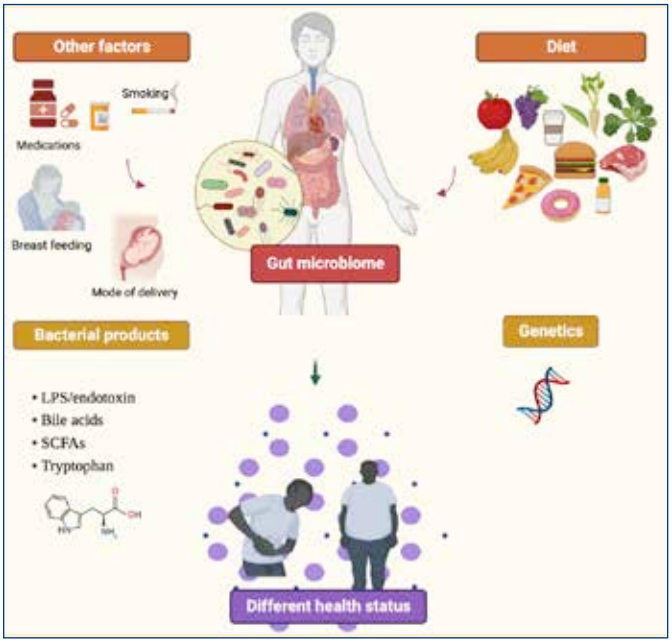
ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract. Patients with IBD are at risk of malnutrition and growth failure, largely depending upon their disease burden. Growing evidence suggests that diet plays an important role in modulating the intestinal microbiota, gut mucosal barrier and hence the intestinal immune system. Thus, diet is considered a potentially modifiable risk factor in IBD. Over the last decade this has garnered significant interest in nutritional management of IBD. The following review will discuss different dietary interventions in the treatment of IBD, including enteral nutritional therapies and emerging specific diets. Given every patient's unique genetic makeup and microbiome, the optimal therapeutic approach, including the choice of nutritional therapy, should be personalized.

INTRODUCTION

Inflammatory bowel disease (IBD) comprising of Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract. The global burden of IBD has been steadily increasing overtime, with over 6.8 million cases reported globally.[1] The pathogenesis of IBD is multifactorial and involves a complex interaction between genetic and environmental factors, which leads to an altered immune response to gut microbiota (**Figure 1**). Studies have shown that immigrants in industrialized countries have a higher risk of developing IBD as compared to people in their native countries, suggesting environmental factors such as diet and lifestyle play an important role in the pathogenesis of IBD.[1] Certain dietary components are considered more pro-inflammatory than others. In a large systematic review, including 19 studies with 2,609 IBD patients, it was found that diets high in fats, especially omega-6 fatty acids, refined sugars, and meat were associated with increased risk of IBD.[2,3] On the contrary, people who followed diets high in fiber, including fruits and vegetables, had decreased risk of developing IBD. Although the exact mechanism is unknown, it is postulated that diet influences changes in the gut microbiome which may affect epithelial barrier function. This in turn seems to have a direct influence on immune function, triggering a pro-inflammatory environment that is characterized by an imbalance in the T-helper17 cell to regulatory T-cell ratio.[4] In a study by Chassaing et al, emulsifiers present in processed foods were shown to increase bacterial translocation and induce low-grade inflammation and metabolic syndrome in wild-type mice and were shown to promote robust colitis in predisposed mice.[5] It has been shown that the gut microbiome in patients with IBD has an overall decrease in microbial diversity. There are decreased numbers of short chain fatty acid (SCFA) producing species, changes in amino acid profile and bile acid dysregulation. These microbial products promote mucus production, strengthen the epithelial barrier, and promote development of T regulatory cells, which in turn suppresses inflammation. Thus, the loss of symbiotic species and microbiota-derived metabolites may have deleterious effects in IBD.[6] In recent years, the role of diet in IBD has sparked special interest and there have been numerous publications regarding the therapeutic role of diet in IBD. In this review, we present a summary of commonly used nutritional therapies for the management of IBD.

Figure 1. Influence of diet and environmental factors on gut microbiome in health and disease



(LPS: lipopolysaccharide, SCFAs: short chain fatty acids)
(Image created with biorender.com)

ENTERAL NUTRITION THERAPIES

Exclusive enteral nutrition (EEN)

Exclusive enteral nutrition (EEN) is one of the most widely studied nutritional support therapies for the treatment of Crohn's disease. **Table 1** summarizes the recent studies on use of EEN in IBD. EEN is recommended as first-line therapy, according to North American and European Pediatric Gastrointestinal Societies, to induce remission in children with active luminal CD (including with colonic involvement).[7] EEN typically involves the use of a complete liquid diet, with the exclusion of normal dietary components for a period of 6–12 weeks. Different formulas may be tried depending upon protein source and are classified into amino acid based (elemental), oligo/dipeptide based (semi elemental) and whole protein based (polymeric). EEN is postulated to work by modulation of gut microbiome by elimination of dietary antigens, improved intestinal epithelial barrier, and resultantly decreased inflammatory mediators.[8] In a study by Borelli et al, 37 children were randomized to two treatment arms, out of which 19 received polymeric formula and 18 received corticosteroids. At week 10, patients in both groups achieved comparable clinical remission. However, children in the polymeric group achieved higher mucosal healing as compared to the corticosteroid group (74% versus 33% respectively; $p < 0.05$).[9]

In a large systematic review with meta-analysis, 18 studies comparing exclusive enteral nutrition to corticosteroids in inducing remission in pediatric CD were included. Authors found that EEN had similar efficacy to steroids in inducing clinical remission. However, patients in the EEN group had higher mucosal healing ($p < 0.0005$), histological healing ($p= 0.0009$) and higher weight gain ($p= 0.05$) in comparison to steroids.[10]

EEN therapy is also associated with fewer side effects versus steroids. More recently, the GROWTH CD study, prospectively followed 147 children with mild-to-moderate CD for 2 years to evaluate complications, steroid-free remission and growth rates. Children treated with EEN had a trend towards higher height Z-scores when compared with children treated with steroids with no difference in relapse rates.[11] Other studies have also compared the effectiveness of EEN to biologic therapy and have found that both treatments lead to improvement in clinical symptoms, mucosal healing, and weight. However, EEN was deemed superior in terms of its side effect profile when compared with infliximab therapy.[12]

While the data for use of EEN in pediatric population is more robust,[11-16] for adults with IBD, EEN has shown variable results.[17-19] A recent 2018 Cochrane systematic review including 27 studies favored steroids over EEN in adults based on intention-to-treat analysis. In adults, 50% of patients on EEN achieved remission versus 83% in pediatrics. It is unclear whether the difference between efficacy in pediatric and adult EEN studies are related to disease severity or compliance with therapy.[20]

Another recent meta-analysis involving adult patients evaluated the benefit of Infliximab and EN (enteral nutrition) with infliximab (IFX) monotherapy for the maintenance of

Table 1. Summary of studies using exclusive enteral nutrition in inflammatory bowel disease

Authors	Year	Age (yr)	Study Design	n	Summary
Borrelli et al [9]	2006	4–17	Randomized control trial	37	EEN therapy achieved similar clinical response to steroids. Mucosal remission higher in steroid group ($p <0.05$)
Buchanan et al [13]	2009	9–13	Prospective study	114	EEN induced clinical remission in 80% cases ($p<0.001$) Disease phenotype should not influence outcomes on EEN.
Grogan et al [14]	2012	5–16	Randomized control trial	34	Choice of formula in EEN (elemental vs polymeric) does not influence remission rates. Fecal calprotectin levels decreased in both groups ($p<0.05$)
Lee et al [15]	2015	3–18	Prospective cohort	90	EEN and anti–TNF were effective for decreasing mucosal inflammation ($p=0.001$) and improving quality of life.
Grover et al [16]	2016	<16	Prospective cohort	54	Use of EEN improved clinical symptoms. Early mucosal healing predicted sustained remission up to 3 yrs ($p=0.005$)
Luo et al [12]	2017	5–15	Prospective cohort	26	Both EEN and infliximab therapy induced clinical remission ($p<0.001$) Less adverse effect profile observed with EEN.
Dolev et al [11]	2018	4–17	Prospective cohort	285	EEN therapy achieved higher remission and better growth vs steroids ($p=0.05$)
Yang et al [19]	2017	18–60	Prospective study	41	EEN effective in inducing clinical remission ($p<0.01$), mucosal healing, and promoting fistula closure.
Heerasing et al [20]	2017	28–50	Retrospective case control	51	EEN improved inflammation ($p=0.02$), reduced need for surgery and post op complications ($p=0.04$)
Sahu et al [21]	2021	22–47	Randomized open label trial	16	EEN use reduced inflammatory burden and improved steroid responsiveness ($p=0.04$)

(EEN: exclusive enteral nutrition, TNF: tumor necrosis factor)

clinical remission and found that rate of clinical remission in patients receiving EN with IFX was 69.4% versus 45.4% in those with IFX monotherapy.[21]

Although successful, EEN is a restrictive diet with limited tolerability, particularly in adults. These challenges in the use of EEN in adults have sparked interest in the use of alternate effective dietary therapies that may be more acceptable and palatable.

Partial enteral nutrition

Partial enteral nutrition (PEN) relies on the use of formula in addition to an unrestricted diet with the aim of improving dietary compliance in patients, especially in adults. In a randomized control trial, Takaji et al evaluated the role of half elemental diet in adults with Crohn's disease and found that the relapse rate in the PEN group was lower [34.6% vs. 64.0%] as compared to the free diet group over a two-year period.[22]

Studies have shown that even though partial enteral nutrition helps in achieving clinical remission, the response is less robust when compared to total enteral nutrition and anti-TNF therapy. In a prospective study of children initiating PEN, EEN, or anti-TNF therapy for Crohn's disease, clinical response was achieved in majority of patients on EEN (88%) and anti-TNF (84%) as compared to 64% on PEN (p trend=0.08).[23] Similarly in another large study, remission rate with PEN was lower than with EEN (15% vs 42%; p=0.035). Although PCDAI fell in both groups (p=0.001), the reduction was greater with EEN.[24]

Both these pediatric studies show that even though partial enteral nutrition helps in controlling symptoms to some extent, exposure to dietary antigens from unrestricted diet may be responsible for the suboptimal response. This has led to trials of specific dietary therapies in the treatment of IBD.

SPECIFIC DIETARY THERAPIES

Specific carbohydrate diet (SCD)

SCD excludes most carbohydrates from the diet, including refined sugars, grains, processed foods, additives and dairy, and allows some specific fermented yogurt and hard cheeses. It excludes disaccharides and most polysaccharides (such as starches) which are thought to be fermented by colonic bacteria and lead to dysbiosis and inflammation. SCD has been effectively studied for induction of remission in IBD, especially in the pediatric population.

In a prospective study of pediatric patients with mild-to-moderate IBD, SCD was associated with clinical improvement and decrease in inflammatory markers. Fecal microbiome reflected these changes with increased microbial diversity.[25] In one large, randomized control trial comparing SCD to modified SCD (mSCD) and whole foods' (WF) diet, patients were evaluated at baseline, 2, 4, 8 and 12 weeks. At week 12, all participants who completed the study achieved clinical remission. The inflammatory markers including C-reactive protein and ESR decreased from baseline in all groups, but more so in SCD and mSCD groups, along with changes in microbial diversity.[26] Despite showing promising results,[25-27] SCD may be very restrictive for pediatric patients to follow with concerns for macro- and micronutrient deficiencies.

Although there are few studies on efficacy of SCD in adult patients, one anonymous online survey of IBD patients (both UC and CD) evaluated the effect of SCD on symptom profile. In the survey, most patients perceived clinical improvement in their IBD symptoms. About 33% of patients reported remission at 2 months after initiation of the SCD and 42% at both 6 and 12 months.[28]

Crohn's disease exclusion diet (CDED)

CDED is a whole food-based diet that avoids dairy, gluten, processed meats, alcohol, emulsifying agents and other foods thoughts to cause dysbiosis, but allows fish, eggs, lean meat, and most fruits and vegetables. The CDED is generally divided into two 6-week phases grouped together as the induction phase, followed by a maintenance phase. CDED is considered to eliminate exposure to dietary antigens that may have adverse effects on epithelial integrity and microbial diversity.

Levine et al performed a randomized study including children with mild-to-moderate CD and followed them for 12 weeks. Children were randomly assigned to two groups: one group received CDED plus 50% of PEN for 6 weeks followed by CDED with 25% PEN for the next 6 weeks. The second group received EEN for 6 weeks followed by free diet with 25% PEN for the next 6 weeks. CDED and PEN was better tolerated versus EEN alone (97% vs 73%, p = 0.002). At week 12, about 75% patients in CDED plus PEN were in corticosteroid-free remission vs 59% children in EEN plus free diet group (p= 0.01). Both groups had reductions in C-reactive protein (CRP) and fecal calprotectin by week 6. However, after the introduction of the free diet in the EEN group, both CRP and fecal calprotectin trended upwards along with a shift of the microbiome towards more pathobionts.[29] In another RCT by Signal Boneh et al, CDED was found to be as effective as EEN to induce remission.[30]

Although there is some evidence that CDED with PEN can be effective for induction of remission in children with mild-to-moderate Crohn's disease, there is not enough data in adults. In one open-label pilot randomized trial, adult patients were randomly assigned to the CDED plus PEN or CDED only group. At week 6, the majority of patients in the CDED plus PEN group had achieved clinical remission when compared to CDED group (68% vs 57%; p=0.46). However, only about 35% of patients achieved endoscopic remission at week 24.[31] The results are encouraging but more clinical data is needed to determine the efficacy of this diet.

Table 2. Summary of specific diet therapies in inflammatory bowel disease

Author	Year	Age (yrs)	Study Design	n	Summary
SCD					
Suskind et al [28]	2016	20–52	Online survey	417	Majority of respondents (42%) perceived clinical benefit to SCD
Obih et al [27]	2016	4–19	Retrospective study	26	Significant improvement in PCDAI, CRP, and calprotectin over time in SCD and controls (p 0.03)
Suskind et al [25]	2018	8–21	Prospective study	13	Patients on SCD had clinical improvement and microbiome shifts. ESR/CRP decreased in most patients (p<0.05)
Suskind et al [26]	2020	7–18	Randomized control trial	18	Lab markers improved in all groups along with microbial diversity. Changes in metabolite profile in SCD, mSCD group (p<0.05)
CDED					
Levine et al [29]	2019	10–17	Randomized control trial	74	Both EEN and CDED+PEN induced remission but the latter was associated with more tolerability (p 0.002), higher sustained remission (p0.01) and microbial shifts.
Sigall Boneh et al [30]	2020	11–17	Randomized control trial	73	CDED+PEN induced clinical remission and improved CRP as early as week 3 of treatment (p<0.01)
Yanai et al [31]	2021	18–55	Randomized open label trial	44	CDED+PEN effective in inducing remission in biologic naive adult pts with mild-to-moderate Crohn's disease (p 0.4)
MD					
Khalili et al [32]	2020	45–79	Prospective cohort	83147	Greater adherence to a Mediterranean diet was associated with a significantly lower risk of later-onset CD (p 0.03)
Lewis et al [34]	2021	27–53	Randomized control trial	194	Both MD and SCD were efficacious in inducing remission (43.5% vs 46.5%: p 0.77). MD easier to follow.
AID					
Olendzki et al [35]	2014	19–69	Case series	40	After following the IBD-AID, all (100%) patients were able to discontinue at least one of their prior IBD medications, and all patients had symptom reduction.
AIP					
Konijeti et al [36]	2017	19–60	Prospective study	15	Dietary elimination improved symptoms (p < 0.01) and endoscopic inflammation in patients with IBD.
CD TREAT					
Svolos et al [37]	2019	>18	Randomized control trial	25	CD-TREAT was easier to comply, replicated EEN changes in the microbiome (p<0.001), and found to be potentially effective in adult patients with active CD.
Svolos et al [37]	2019	6–15	Open label trial	5	Baseline PCDAI decreased in CD-TREAT group (p=0.05) along with decrease in fecal calprotectin (p 0.002)
Low FODMAP					
Pedersen et al [39]	2016	20–70	Randomized control trial	89	Low FODMAP diet reduced IBS-like symptoms (p 0.02) and increased quality of life (p < 0.01) in patients with IBD in remission.
Cox et al [38]	2020	27–57	Single blind trial	52	4-week diet low in FODMAPs decreased persistent gut symptoms in patients with quiescent IBD (p 0.007)

(SCD: Specific carbohydrate diet, mSCD: modified specific carbohydrate diet, CDED: Crohn disease exclusion diet, MD: Mediterranean diet, AID: Anti-inflammatory diet: AIP: Autoimmune protocol, CD-TREAT: Crohn's disease treatment with eating diet, FODMAPs : Fermentable oligosaccharides, disaccharides, monosaccharides, polyols, PEN: partial enteral nutrition, EEN: exclusive enteral nutrition, CRP: C reactive protein, ESR erythrocyte sedimentation rate, PCDAI: pediatric Crohn's disease activity index)

Mediterranean diet (MD)

Mediterranean diet mainly consists of fish, legumes, whole grains, fruits, and vegetables. It involves consumption of olive oil and nuts as source of fat. This diet is high in omega-3 fatty acids which are though to play a protective role in inflammation. Numerous cohort studies, randomized controlled trials, and systematic review have documented the efficacy of this diet to reduce inflammation.

In a prospective cohort study of 83,147 participants, adherence to MD decreased the risk of developing CD overtime (p= 0.03).[32] In another study, patients with UC who underwent pouch surgery and adhered to MD had lower inflammatory burden including reductions in CRP, ESR, and fecal calprotectin. In a subgroup of patients, higher adherence to MD decreased the risk of later onset of pouchitis, thus modifying intestinal inflammation in IBD.[33]

In a large, randomized control trial of 194 adult patients with CD, the effect of MD was compared to SCD for a period of 12 weeks. Participants in both groups achieved clinical remission (SCD 46.5% vs MD 43.5%; p = 0.77) Fecal

calprotectin response was achieved in 34.8% patients in the SCD group vs 30.8% in the MD group (p = 0 .83). None of the diets were superior to another in inducing clinical remission. This study concluded that given greater ease of following MD along with other numerous health benefits, MD may be preferrable to SCD for most patients with CD and mild-to-moderate symptoms.[34]

IBD Anti-inflammatory diet (AID)

AID was developed by a group at the University of Massachusetts medical school. It is derived from SCD and is based on eliminating certain foods thought to be pro-inflammatory. It limits certain carbohydrates (lactose and refined carbs) as well as total and saturated fats, and encourages use of omega-3 fatty acids, as well as relies on use of prebiotics/probiotics to help restore balance of intestinal flora. In a case series of 40 adult patients with IBD, after following the IBD AID, 100% patients were able to discontinue at least one of their prior IBD medications, with improved bowel frequency in most patients. This study, however, did not assess inflammatory markers or endoscopic remission after treatment. There is no current data to support the use of the IBD-AID in children. Future prospective studies are needed to determine the value of this diet in the pediatric population.[35]

Autoimmune protocol (AIP)

Autoimmune protocol is derived from the paleolithic diet. It includes lean meat, fish, vegetables, nuts, and seeds, and eliminates processed foods like refined sugars and gluten that may be antigenic and promote inflammation. This diet consists of initial elimination phase followed by a reintroduction and a maintenance phase. There haven't been many studies on the use of AIP in IBD. In one study, adult patients with IBD who received AIP diet showed improvement in clinical symptoms along with improvements in fecal calprotectin and scoring parameters on follow-up endoscopy. However, none of the patients had complete resolution of symptoms. This study was limited by small sample size and lack of randomization.[36]

Crohn's disease treatment with eating diet (CD-TREAT)

The CD-TREAT is similar to EEN and involves exclusion of certain dietary components (like lactose, gluten, alcohol, emulsifiers) and matches macronutrients and micronutrients to the composition of commonly used EEN formula: Modulen. The aim of using CD-TREAT is to enhance the tolerance and compliance by using a whole food-based diet. In a RCT[37], 25 healthy adults were randomly assigned to EEN or CD-TREAT for 1 week. CD-TREAT was found to be more tolerable than EEN and induced similar effects to EEN on fecal microbiome composition and resultant metabolome profile. In subsequent open label study, 5 children with active CD received CD-TREAT and their clinical activity and calprotectin were evaluated after 8 weeks of treatment. In children receiving CD-TREAT, 4 (80%) had a clinical response and 3 (60%) entered remission, with significant decreases in fecal calprotectin (p= 0.002).[37]

Results from the CD-TREAT study provided promising results that individualized diets can be used to target changes in gut inflammation.

Low Fermentable oligosaccharides, disaccharides, monosaccharides, polyols (FODMAP) diet

Low FODMAP diet is one of the extensively studied diets for the treatment of irritable bowel syndrome. It is postulated that FODMAPs induce symptoms via osmotic load and colonic gas production in the setting of visceral hypersensitivity. In a single-blind trial of 52 patients with IBD and persistent gut symptoms, a higher proportion of patients reported relief of gut symptoms following the low FODMAP diet (52%) vs the control diet (16%). However, microbiome diversity and markers of inflammation did not differ significantly between groups.[38]

In another RCT of patients with IBD in remission or with mild-to-moderate disease and coexisting IBS-like symptoms, low FODMAP diet resulted in overall symptom reduction.[39]

Both studies conclude symptoms improvement but the data on whether it impacts IBD is inconclusive.

CONCLUSION

Diet seems to have a crucial role in the pathogenesis and treatment of IBD. While some therapies like enteral nutrition therapy are extensively studied and considered effective in inducing remission especially in children, clinical data regarding regular dietary therapies for induction and maintenance of remission of IBD is evolving. Specific diets that have shown promise include SCD, CDED+PEN and MD. However, further larger scale randomized trials are needed before we can assess their long-term benefit. Factors like growth potential and pubertal progression should be considered in children when deciding choice of therapy. Dietary therapies should be individualized for patients and must involve shared decision making between patients, dietitians, and their physicians.

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Authors

Rahiya Rehman, MD, Division of Pediatric Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

Beth Pinkos, MS, RDN, Division of Pediatric Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

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

Carolina Cerezo, MD, Division of Pediatric Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

Correspondence

Carolina Cerezo, MD
593 Eddy Street, Providence, Rhode Island 02903
ccerezo@lifespan.org

Lessons Learned from the Ocean State Crohn's and Colitis Area Registry

JASON M. SHAPIRO, MD; NEAL S. LELEIKO, MD, PhD; BRUCE E. SANDS, MD; SAMIR A. SHAH, MD

The Ocean State Crohn's and Colitis Area Registry (OSCCAR) is a prospective, community-based cohort of adult and pediatric patients diagnosed with inflammatory bowel disease (IBD) in Rhode Island (**Figure 1**). A total of 408 patients with Crohn's disease (CD), ulcerative colitis (UC) or IBD-unclassified (IBD-U) were enrolled between 2008 and 2013. Clinical follow-up of the cohort continued through December 2018. Funding was initially provided by the National Institutes of Health (R21DK078555-025) with follow-up support from the Crohn's and Colitis Foundation through a grant from the Centers for Disease Control and Prevention (5U01DP000340-03).

The original study objectives of OSCCAR were to[1]:

1. Establish study procedures to found and maintain a population-based, prospective inception cohort of IBD patients in the state of Rhode Island.

2. Determine the incidence rates of Crohn's disease and ulcerative colitis in Rhode Island and to extrapolate these rates to the general population of the United States.

3. Define the natural history of IBD in the setting of contemporary treatment practices in the US, and to obtain preliminary data to identify clinical and subclinical factors associated with disease progression in Crohn's disease and ulcerative colitis.

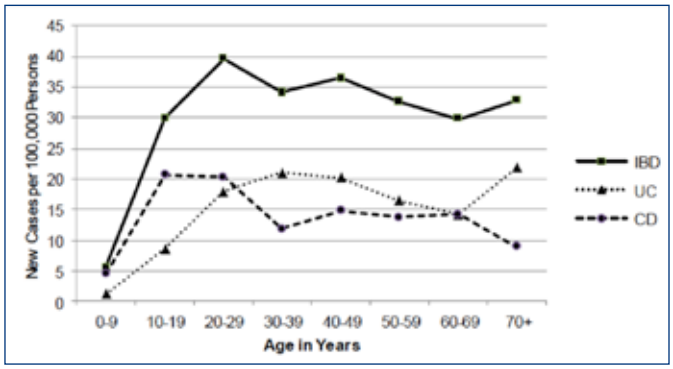
4. Identify clinical and subclinical (including genetic) risk factors for steroid resistance in IBD.

To accomplish these goals, detailed demographic, serologic, radiographic, endoscopic, pathologic, and surgical data were prospectively obtained. Validated measures of disease activity, quality of life, and emotional health were also collected. Biospecimens including blood, urine and stool were prospectively banked for future analyses. The robust OSCCAR dataset has since served as the substrate for a number of clinical and translational projects, the majority involving trainees. This article will summarize how these collective studies have added to the IBD literature.

INCIDENCE OF IBD IN RHODE ISLAND

The global incidence of IBD in children and adults has been increasing at an alarming rate.[2,3] Population-based data from the United States was previously limited to reports from Olmsted County, Minnesota and Northern California.[4,5] One of the main objectives of OSCCAR was to determine the incidence of IBD in Rhode Island. When recruitment began, 97 of 98 practicing gastroenterologists in RI agreed to refer patients for enrollment. In addition, 11 practices in Massachusetts and Northern Connecticut that cared for RI residents were included. Exhaustive review of administrative billing data was performed to calculate the age and sex-adjusted incidence of IBD in RI from January 2008 through December 2010.[6] During this 3-year time frame, 971 residents were diagnosed with IBD including 444 with CD, 486 with UC and 41 with IBD-U. Of these patients, 291 (30%) were enrolled in OSCCAR. The median age at diagnosis was 35 for CD and 44 for UC. A total of 110 children were diagnosed with IBD with 84 (76%) enrolled in OSCCAR. The estimated annual incidence of IBD from 2008-2010 was 30.2 per 100,000 persons (**Figure 2**). Extrapolated, this would translate to more than 90,000 new IBD cases per year in the US. These rates were significantly higher than previously published epidemiologic

Figure 2. Age-specific incidence per 100,000 persons among the total population of Rhode Island between 2008–2010.



Adapted from Shapiro, et al. Inflamm Bowel Dis 2016.

data from Olmsted County and Northern California, which were obtained from review of a central medical record system and insurance claims database, respectively. In contrast to these studies, our RI data was reflective of nearly all new diagnoses in the state. This is based on our rigorous auditing of medical records from the majority of GI practices caring for residents over the timeframe of interest. The higher incidence we observed in RI was likely multifactorial, including a true rise in incidence and advantages of the well-defined geography of our state compared to larger populations in Olmsted County and Northern California, where capturing each individual diagnosis represents significant methodological challenge. Furthermore, the comparison reports from Minnesota were based on data from 1990–2000 and Northern California from 1996–2002. Thus, our higher rates are consistent with worldwide trends noting a general increase in IBD over time. We are currently in the process of re-calculating the state-wide incidence of IBD over the last 5 years, with a specific interest in how the COVID-19 pandemic has impacted trends.

CLINICAL LESSONS FROM OSSCAR

Presenting Symptoms

IBD can have a profound impact on a patient's physical and emotional health. An early study of 220 patients revealed that 26.4% reported significant fatigue at diagnosis, regardless of disease activity.[7] Fatigue was strongly associated with poor health-related quality of life, disability and depression. A follow-up study evaluating presenting symptoms within 4 weeks of IBD diagnosis was completed utilizing a 41-question symptom inventory.[8] Data from 223 patients with CD and 150 patients with UC were analyzed. Fatigue and abdominal pain were the most common presenting symptom in CD with rates of 80.6% and 80.4%, respectively. The most common symptoms in UC were passage of blood with bowel movements (86.6%) and loose/watery bowel movements (86.5%). This study represented one of the most extensive evaluations of presenting symptoms in IBD, to date.

Clostridium difficile Screening

Chronic diarrhea is a common presenting symptom of IBD. *Clostridium difficile* is a common cause of infectious diarrhea, with increased prevalence in patients with IBD. Testing for CDI is considered standard of care in the initial workup of patients with recurrent diarrhea, especially prior to initiation of immunosuppressive therapies. Of 320 patients enrolled in OSSCAR, 227 (70.9%) reported diarrhea as a presenting symptom.[9] Only 113 (49.8%) had CDI testing, 5% of which yielded a positive result. CDI, in addition to causing a flare of IBD symptoms, can lead to worse outcomes and hence testing for CDI in the context of a new diagnosis or symptomatic flare is an important quality measure. Over time, an increase in appropriate testing for CDI was observed. These quality assurance results were utilized to increase provider education regarding the importance of CDI testing in symptomatic patients with known or suspected IBD.

Body Image and Sexual Functioning

IBD and treatments such as corticosteroids can have a profound impact on a patient's quality of life (QOL). Body image dissatisfaction (BID) in IBD was assessed in 274 adult patients with a minimum of 2 years of follow-up via a modified version of the Adapted Satisfaction with Appearance Questionnaire.[10] Female sex, prolonged steroid exposure, co-morbid musculoskeletal complaints, ileocolonic disease location in CD, higher disease activity and higher symptom burden were all associated with greater BID. Greater BID was associated with lower health-related quality of life. Separate studies were completed examining sexual functioning in adult males and females, also with greater than 2 years of clinical follow-up.[11,12] Of 116 eligible female patients, 97% reported sexual dysfunction that did not improve with IBD treatment over time. Global sexual dysfunction and erectile dysfunction was reported in 39% and 94% of 69 eligible male patients, respectively. Clinicians should be aware of this impact on sexual functioning, proactively inquire about these issues and refer appropriately to improve QOL.

Radiation Exposure

Diagnostic imaging is integral in the initial evaluation, acute management and long-term follow-up of patients with IBD. In an effort to minimize radiation exposure, magnetic resonance enterography (MRE) has replaced the CT scan and upper GI with small bowel follow through as the preferred, non-urgent imaging modality in IBD. A study from OSCCAR of 207 patients with Crohn's disease and 120 with ulcerative colitis was completed to identify those at risk for significant radiation exposure.[13] Those with CD were more like to have a CT compared to UC. Children had less CT scans, overall. Risk factors for increased radiation exposure in our cohort included history of prior gastrointestinal surgery, being treated with biologic therapy such as infliximab, pain-predominant symptoms and isolated ileal disease. Not surprisingly, patients with stricturing or penetrating Crohn's disease phenotype had higher radiation exposure compared to those with non-stricturing, non-penetrating inflammatory disease. Given the potential harms of radiation, measures to minimize radiation to patients younger than 45, including educating emergency room providers and patients, are critical.

Opportunistic Screening for Bone Disease in IBD

Osteopenia and osteoporosis are prevalent among patients with IBD.[14] Regular bone density screening is recommended

as part of routine IBD health maintenance, but not always completed.[15] Evaluating attenuation of the lumbar spine from CT scans can provide rudimentary information regarding a patient's bone health. To further assess, CT scans from 105 patients were retrospectively evaluated.[16] 72.4% were noted to have "normal" bone mineral density with 27.6% noted to be potentially osteopenic. Sixty patients had more than 2 CT scans over the study time frame. A decrease in bone density over time was observed with mean loss of 9.3 Hounsfield units. A non-significant decrease in BMD was noted in patients exposed to greater than 31 days of corticosteroids. A follow-up study is currently underway examining rates of sarcopenia in IBD patients utilizing standardized measures of psoas muscle thickness from CT scans.

Corticosteroid Use

Systemic corticosteroids (CS) such as prednisone are a mainstay of treatment in patients newly diagnosed with IBD. OSCCAR began enrollment during a time when providers were becoming more comfortable with biologic medications such as infliximab and adalimumab. Prior reports noted rates of CS exposure during the first year of diagnosis ranging from 39–75% with surgical resection rates as high as 13–18% in the same time frame.[17-20] Examining 272 patients enrolled in OSCCAR, we observed that 60% of CD and 57% UC were exposed to at least one course of CS in year 1.[21] However, only 2% of patients required surgical resection during the same timeframe. 22% of patients treated with CS in year one were also treated with a biologic agent targeting tumor necrosis factor alpha (TNF-a). This observation is consistent with recent reports demonstrating that early biologic use is associated with decreased surgery risk.[22,23]

TRANSLATIONAL STUDIES

OSCCAR was one of the first prospective IBD registry studies to bank biosamples. In fact, OSCCAR stool samples were included in one of the earliest reports describing the role of microbial metabolism in IBD pathogenesis.[24] Additional translational studies are outlined below.

Serum Proteomics

A number of patients with CD present with stricturing disease or develop intestinal strictures over time. Serum samples from OSCCAR were used in a pilot study examining proteomic profiles of patients with this severe phenotype.[25] Serum from 9 patients with stricturing CD post-resection, 9 patients with non-stricturing CD and 9 UC controls were analyzed via liquid chromatography mass spectrometry. Significant differences were noted in proteins and peptides between the 3 groups. Proteins associated with complement activation, fibrinolytic pathways and lymphocyte adhesion were noted in patients with stricturing disease phenotypes. A follow-up study is currently underway using serum from OSCCAR and a separate Pediatric CD cohort to discover and validate blood protein biomarkers of anti-TNF response in patients with CD.

Stool Immunoglobulin A

IBD pathogenesis has been attributed to a combination of genetic susceptibility, alterations in the intestinal microbiome and putative environmental triggers.[26] The complex interaction between the mucosal immune system and intestinal microbiota is integral to understanding mechanisms of inflammation in IBD.[27] A pilot study suggested that bacteria heavily coated with immunoglobulin A (IgA) promote a pro-inflammatory state in IBD.[28] To further explore this, a combination of bacterial cell sorting and 16S rRNA gene sequencing – a technique referred to as IgA-SEQ – was used to analyze IgA-coating in the stool of 184 patients from OSCCAR and 32 healthy controls.[29] IgA-SEQ identified unique bacteria in IBD not otherwise noted using basic 16S sequencing techniques. Patients treated with anti-TNFs were noted to have altered microbiota-specific IgA response. In addition, IgA coating of a specific bacteria (*Oscillospira*) was associated with delay in time to surgery. Future work hopes to explore the potential of IgA-SEQ in biomarker discovery and novel, microbial-based therapeutic approaches.

CONCLUSION

OSCCAR has supported a variety of clinical and translational research projects over the past 10 years. The impact of OSCCAR, however, transcends a project or publication. OSCCAR has been a valuable resource for trainees at all levels from a range of disciplines. Medical students, residents, fellows, graduate students and junior faculty have been involved in every published study, many as first author. In fact, a number of the accomplished authors contributing to these articles were involved in OSCCAR at various points in their careers. This is a testament to the lasting impact OSCCAR has had on the IBD community at large. While the study closed in 2018, these collaborative relationships endure as we continue to work on existing projects and consider future studies.

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Authors

Jason M. Shapiro, MD, Warren Alpert Medical School of Brown University, Division of Gastroenterology, Nutrition and Liver Diseases, Hasbro Children's Hospital, Providence, Rhode Island.

Neal S. LeLeiko, MD, PhD, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Columbia University, New York-Presbyterian Morgan Stanley Children's Hospital, New York, New York.

Bruce E. Sands, MD, Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York.

Samir A. Shah, MD, Warren Alpert Medical School of Brown University, Chief of Gastroenterology, The Miriam Hospital, Providence, Rhode Island.

Correspondence

Jason M. Shapiro, MD
Associate Professor of Pediatrics and Medicine
Director, Pediatric Inflammatory Bowel Disease Center
Division of Pediatric Gastroenterology, Hepatology and Nutrition
Hasbro Children's Hospital/Rhode Island Hospital
Warren Alpert Medical School of Brown University
Providence, Rhode Island 02903
401-444-8306
Fax 401-444-8748
jason_shapiro@brown.edu

Effects of COVID-19 on Patients with Inflammatory Bowel Disease

LAWRENCE KOGAN, MD; RYAN C. UNGARO, MD; FREDDY CALDERA, MD; SAMIR A. SHAH, MD

ABSTRACT

Patients with inflammatory bowel disease (IBD) may take medications that affect their immune system, altering their ability to fight infection or making them less responsive to vaccines. Many of these patients were excluded from original studies regarding COVID-19, which creates a challenge for gastroenterologists to use evidence-based medicine to guide their management. We reviewed the available literature regarding patients with IBD and COVID-19 outcomes and response to vaccinations. Of all IBD patients, 0.3–24% acquired COVID-19 infection and 7–67% of those patients required hospitalization. Many studies have analyzed the effects of COVID-19 on patients with IBD. Observational studies suggest most IBD patients are not at higher risk from COVID-19 infection and that the COVID-19 vaccines are safe, effective and recommended. However, patients being treated with a TNF-α inhibitor with an immunomodulator and patients being treated with steroids should be monitored closely and efforts should be made to wean patients off of systemic steroids if possible. Patients treated with these regimens had lower antibody responses to vaccination and were at higher risk of acquiring severe COVID-19 infection. Antibody responses were robust after the second dose of mRNA vaccines with 85–100% of individuals showing seroconversion, albeit with lower levels of antibodies compared to the general population.

KEYWORDS: Inflammatory Bowel Disease, COVID-19, Vaccination

INTRODUCTION

Since its discovery at the end of 2019, COVID-19, caused by the SARS-CoV-2 virus, has created a global pandemic. Although most cases of the disease are asymptomatic or mild, the sheer number of moderate or severe cases has at times overwhelmed the healthcare system, with large numbers of hospitalizations, reallocation of healthcare resources, and delays in routine care such as colonoscopies.[1] The creation of COVID-19 vaccines and treatments has improved our management of the disease, but the virus still has the potential to cause substantial harm.[2]

Inflammatory Bowel Disease (IBD), encompassing Crohn's Disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition that affects at least 3 million Americans.[3] Since patients with IBD are frequently on immunosuppressive medications, there has been concern about how COVID-19 may impact IBD patients, including whether they are at higher risk of infection as well as whether a COVID-19 infection, which can present with gastrointestinal symptoms in up to 20% of patients, might mask an IBD flare.[4]

Unfortunately, patients with IBD were excluded from the original randomized control trials for COVID-19 vaccine efficacy[5,6] and the effect of IBD and medications on vaccine response and clinical outcomes remains a topic of interest for the IBD population. Qualitative studies have identified that patients described a sense of anxiety and uncertainty about whether they are "high risk" with COVID-19, identifying a gap in either knowledge or communication regarding their disease.[7]

Here we review the natural history of COVID-19 infection in patients with IBD, the immune response to COVID-19 vaccines, the safety and adverse events of COVID-19 vaccines, the effect of the vaccine on patients' IBD treatment and the effectiveness of vaccines to prevent severe illness.

METHODS

A comprehensive literature review was performed using PubMed from inception through 10/15/22. No restrictions were applied to language, country of origin or publication date. Keywords used were "inflammatory bowel disease", "Crohn's disease", "Ulcerative Colitis", "seroprevalence", "seroconversion", "vaccine", "vaccination", "coronavirus" and "COVID-19". Primary research was prioritized, but there were no restrictions on study design or statistical analysis. Relevant articles were reviewed with particular attention to adult patients with inflammatory bowel disease, their response to vaccination and their clinical course as a result of the infection.

RESULTS

IBD and COVID outcomes

The prevalence of COVID-19 infection in IBD patients ranges from 0.3% to 24.4%, as seen in **Table 1**.[8-16] Given the wide variation in reported COVID-19 outcomes, it is worth

Table 1. Outcomes of patients with COVID-19

Author	Study Design	Dates of Enrollment	Number of IBD patients	% of IBD patients COVID positive	% of COVID infected patients hospitalized	% of COVID infected patients with severe COVID	% of COVID infected patients who died
Iborra, Puig, et al	Cross-Sectional Observational Study	3/2020–4/2020	234	2.1%			
Zabana, Marin-Jimenez, et al	Registry-Based, Prospective Observational Study	3/2020–7/2020	53682	0.9%	35%	7.9%	3.7%
Norsa, Cosimo, et al	Retrospective Analysis of IBD Patients on Biologics	3/2020–7/2020	90	21.1%	0%		
Lukin, Kumar, et al	Matched Cohort Study		119	24.4%	0%		
Sultan, Mone, et al	Single Center Retrospective Cohort Study	1/2020–10/2020	83	100.0%	67%	14.5%	13.3%
Wetwittayakhlang, Albader, et al	Single Center Prospective Cohort Study	3/2020–4/2021	3516	2.3%	7%	2.4%	2.4%
Ludvigsson, Axelrad, et al	Population Cohort Study	2/2020–7/2020	67292	1.2%	22%	8.0%	6.5%
Lev-Tzion, Focht, et al	Population Based Retrospective Study	12/2020–6/2021	12109	0.3%	0%		
Ricciuto, Lamb, et al	Registry Based Retrospective Cohort Study	3/2020–8/2021	6078	100.0%	15%	4.0%	

noting that there were two large studies which analyzed over 50,000 IBD patients each. Those include the ENEIDA registry in Spain and the Ludvigsson et al population-based cohort study out of Sweden. They estimated the prevalence of COVID-19 infection at 0.9% and 1.2%, respectively, hospitalization at 35% and 22%, and severe COVID-19 (defined by ventilator use, treatment in intensive care or death) at 7.9% and 8.0%, respectively.[8,15] Both studies found that patients with IBD were more likely to be hospitalized compared to the general population, however, without an increased probability of severe infection.

Despite the wide range of reported outcomes, studies suggested that patients with IBD have an equal or lower risk of COVID-19 infection, as well as severe COVID-19, than the general population.[11-13,15] The risk factors for severe COVID-19 in IBD are generally the same as the overall population, which include older age and multiple comorbidities.[13] However, three subgroups of IBD patients have been consistently found to have higher risk of severe COVID-19 infection: those being treated with anti-TNF therapy combined with an immunomodulator, those on corticosteroids, and those with active disease.[13,14,17-19] Interestingly, those treated with anti-TNF monotherapy may have a somewhat lower risk for severe disease.[20]

COVID-19 Vaccine Uptake Among Patients with IBD

Historically, patients with IBD tend to have lower vaccine uptake than the general population, and their uptake of the COVID-19 vaccine has varied widely.[21,22] A single center American study from 2021 found that over one-third of patients are hesitant to get the COVID-19 vaccine, mostly out of concern for vaccine efficacy and side effects.[23] However, vaccination intent may supersede 90% and one center found that 84% of its IBD patients had completed a vaccination series, consistent with the general population.[21,24] This is similar to a British study of over 400 patients with IBD on biologic therapy which found that 95% had completed a two-dose mRNA vaccination series.[25]

Despite the benefits of COVID-19 vaccination in preventing disease, some patients have been averse to COVID-19 vaccination out of concern for adverse events such as causing a flare of their IBD. However, the inflammatory state induced by COVID-19 infection can lead to an IBD flare within 90 days of infection in 7–10% of patients and there has not been elevation in fecal calprotectin or increase in disease activity after vaccination.[13,26-28] Furthermore, the risk of adverse events from the vaccine appears to be similar to the general population, and possibly diminished if a patient is on biologic therapy.[29,30] A large multicenter observational cohort study showed that injection site tenderness was the most common localized reaction and fatigue was the most common systemic reaction. Following vaccination, severe adverse events were rare and only 2% of patients suffered from an IBD flare during the follow-up period.[27] Compared to unvaccinated individuals, the incidence of flares is the same in patients who received two doses of an mRNA vaccine.[11]

Vaccine-Induced Immune Response to COVID-19 vaccine

As with the general population, the vaccine has proven to be effective at inducing antibody production and preventing severe disease in patients with IBD. After the second dose

Table 2. Vaccine Efficacy in Patients with IBD

Authors	Study Design	mRNA vaccine	Number of IBD patients	Seropositive after 2 doses	Factors that led to lower levels	% anti-TNF therapy	% anti-TNF and IM
Caldera, Knutson, et al	Prospective Cohort Study	100%	122	97%	IM	38%	16%
Cerna, Duricova, et al	Single Center Prospective Cohort Study	52%	602	98%	Anti-TNF+ IM	48%	24%
Edelman-Klapper, Zittan, et al	Multicenter Prospective Controlled Study	100%	185	100%	Anti-TNF	36%	4%
Kennedy, Lin, et al	Multicenter, Prospective Observational Cohort Study	46%	1293	85%	Age >60, IM, CD>UC, Smoking	67%	41%
Alexander, Kennedy, et al	Multicenter, Prospective, Case-Control Study	45%	370	96%	Anti-TNF monotherapy, Anti-TNF + IM, tofacitinib	28%	15%
Wong, Dixon, et al	Prospective Cohort Study	100%	48	100%	Anti-TNF, vedolizumab	33%	0.0%
Vollenberg, Tepasse, et al	Prospective Cohort Study	100%	106	98%	Anti-TNF		
Melmed, Botwin, et al	Prospective Observational Study	100%	582	99%		31%	8.6%
Kappelman, Weaver, et al	Prospective Observational Cohort Study	100%	317	95%	Steroids	42%	7.6%
Tsipotis, Frey, et al	Prospective Cohort Study	100%	217	99%	Anti-TNF+ IM	51%	32%

Key: Immunomodulator (IM)

of the two mRNA vaccine series, 85–100% of patients with IBD showed seroconversion, as seen in **Table 2**, with varying vaccine efficacy based on IBD treatment.[18, 26, 31-38] The lowest rate of seroconversion was seen in the study with the highest proportion of patients on combination anti-TNF and immunomodulator therapy. Despite achieving seroconversion equal to the general population, the absolute antibody level in patients with IBD may be lower, and their immunity may wane faster than the general population.[34, 36, 37]

With regards to vaccine choice, the mRNA vaccines appear to elicit a stronger antibody response than the adenovirus vaccines, and the mRNA-1273 (Moderna) vaccine resulted in higher antibody levels than the BNT-162b2 (Pfizer- BioNTech) vaccine, after the initial series, as well as after a booster shot.[32,37,39] Several studies looked at the antibody response for those who received biologic therapy for their IBD in between their first and second vaccine doses and found no difference in antibody response when compared to individuals who delayed IBD treatment.[33,35]

At a population level, the vaccines were 80% effective at preventing infection in a large cohort of over 14,000 American veterans with IBD.[40]

Pandemic Clinical Impact on IBD

The pandemic has affected patients' adherence to standard regimens of IBD treatment. 8–10% of patients cited fear of going to the hospital as the most common reason for postponing IV infusions.[16,41] In China, over half of IBD patients reported a delay in blood tests, colonoscopy or CT scans.[42] Although specific studies of delays in IBD care in the United States require further investigation, there was a 79% decrease in colorectal screening across the general population during the peak of the first wave, leading to a screening deficit of 3.8 million people.[43] With regards to clinic visits, there was a 4000% increase in telehealth use by gastroenterologists, and this change was accepted by patients.[44,45] Furthermore, the pandemic accelerated trials in Europe of a new subcutaneous infliximab injection, which suggested that this formulation was well tolerated and efficacious without the need to switch the active drug to another drug like adalimumab due to convenience of self-administration.[46]

DISCUSSION

Across several studies, we found that as a whole patients with IBD appear to have similar outcomes to COVID-19 infection compared to the general population and that vaccines are safe and effective, without an increase in adverse effects or likelihood of inducing an IBD flare. This should be reassuring to both providers and patients. However, those with active disease, those being treated with an anti-TNF agent combined with an immunomodulator and those being treated with systemic corticosteroids appear to have both blunted antibody response and increased likelihood of severe COVID-19. Additional data is needed to investigate these findings, as well as the impact of anti-TNF monotherapy on patient outcomes, as this may identify patients that are higher risk and require closer monitoring, increased precautions such as masks or additional interventions such as early or extra booster shots. Furthermore, it is essential to

keep patients' IBD well controlled, as corticosteroids can increase a patient's risk of COVID-19 infection, which, as noted previously, can also lead a patient to flare.

Currently there is very limited data on the effect of booster shots on seropositivity or COVID-19 outcomes for patients with IBD, but it remains a topic of interest with obvious clinical impacts. Recently, bivalent boosters have been developed by both Pfizer-BioNTech and Moderna to target both the original COVID-19 strain and Omicron subvariants, the latter which constitutes a majority of the identified strains in the United States at the time of this article.[47,48] These boosters have been shown to elicit increased antibody responses against Omicron, and although the efficacy at reducing infections in humans is expected, it is too early to know the extent of their effectiveness, particularly in patients with IBD; however, we would expect a similar response to the bivalent vaccines, as that has been seen with previous vaccines. Given that many patients with IBD have waning antibody levels compared to the general population, they should be encouraged to obtain protection against the virus with the most updated vaccine available, with additional encouragement depending on their age and if they are on chronic steroids. (**Table 3**)

Table 3. Take-Home Messages

As a group, IBD patients do just as well with COVID as the general population
Vaccines are safe and effective in patients with IBD
Boosters should be encouraged, but it is unclear whether 4th doses are needed
Guidance is evolving about what do with current IBD regimens, especially if a patient is on combination therapy

Interestingly, the large European studies found much higher frequencies of hospitalizations (22–35%) and severe COVID-19 (7.9–8.0%) than the international SECURE-IBD registry. In SECURE-IBD, providers reported over 6,000 cases of COVID-19 in IBD patients and described rates of 15% hospitalization and 4% severe COVID-19. This most likely reflects the impact of vaccines, as both the Zabana and Ludvisson papers followed patients in 2020, prior to the vaccine rollout. An earlier paper from the SECURE-IBD registry, published in 2020, showed a similar rate of severe COVID-19 (7.8%) as the other large studies.[20] The difference could also be related to reporting biases depending on the availability of testing and the enrollment period, as milder cases may have been missed earlier in the onset of the pandemic.

With regards to management of IBD treatment, if a patient tests positive for COVID-19, additional research is warranted. Consensus guidelines recommend holding immunomodulators and rapidly weaning patients with an active COVID-19 infection off of steroids, if possible, and to resume them 2 weeks after symptoms resolve.[49] For COVID-19 infection that requires hospitalization, patients with IBD should undergo standard treatment for the general population including dexamethasone and remdesevir. For COVID-19 infection that doesn't necessitate hospitalization, some patients may be considered high risk if they are treated with corticosteroids, immunomodulators or anti-TNF agents. If they are considered high risk, they could receive priority for treatments like biologic therapies that are efficacious against local variants, but may have limited availability. While a variety of advanced treatments, such as Nirmatrelvir-Ritonavir (Paxlovid) are available, there may be variable efficacy against different variants and clinicians should be mindful of this before prescribing medications.

Future studies that include patients with inflammatory bowel disease and evaluate not only antibody levels, but clinical outcomes, could help guide management of patients and vaccination protocols.

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Authors

Lawrence Kogan, MD, Clinical Fellow, Department of Digestive Diseases, Yale School of Medicine, New Haven, CT.

Ryan C. Ungaro, MD, The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY.

Freddy Caldera, MD, Associate Professor of Medicine, University of Wisconsin, Madison, WI.

Samir A. Shah, MD, Clinical Professor of Medicine, Alpert Medical School of Brown University; Chief of Gastroenterology, The Miriam Hospital.

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Correspondence

Lawrence Kogan, MD
Clinical Fellow, Division of Digestive Diseases
300 Cedar Street, TAC S-241
New Haven, CT 06510
203-785-7012
lawrence.kogan@yale.edu

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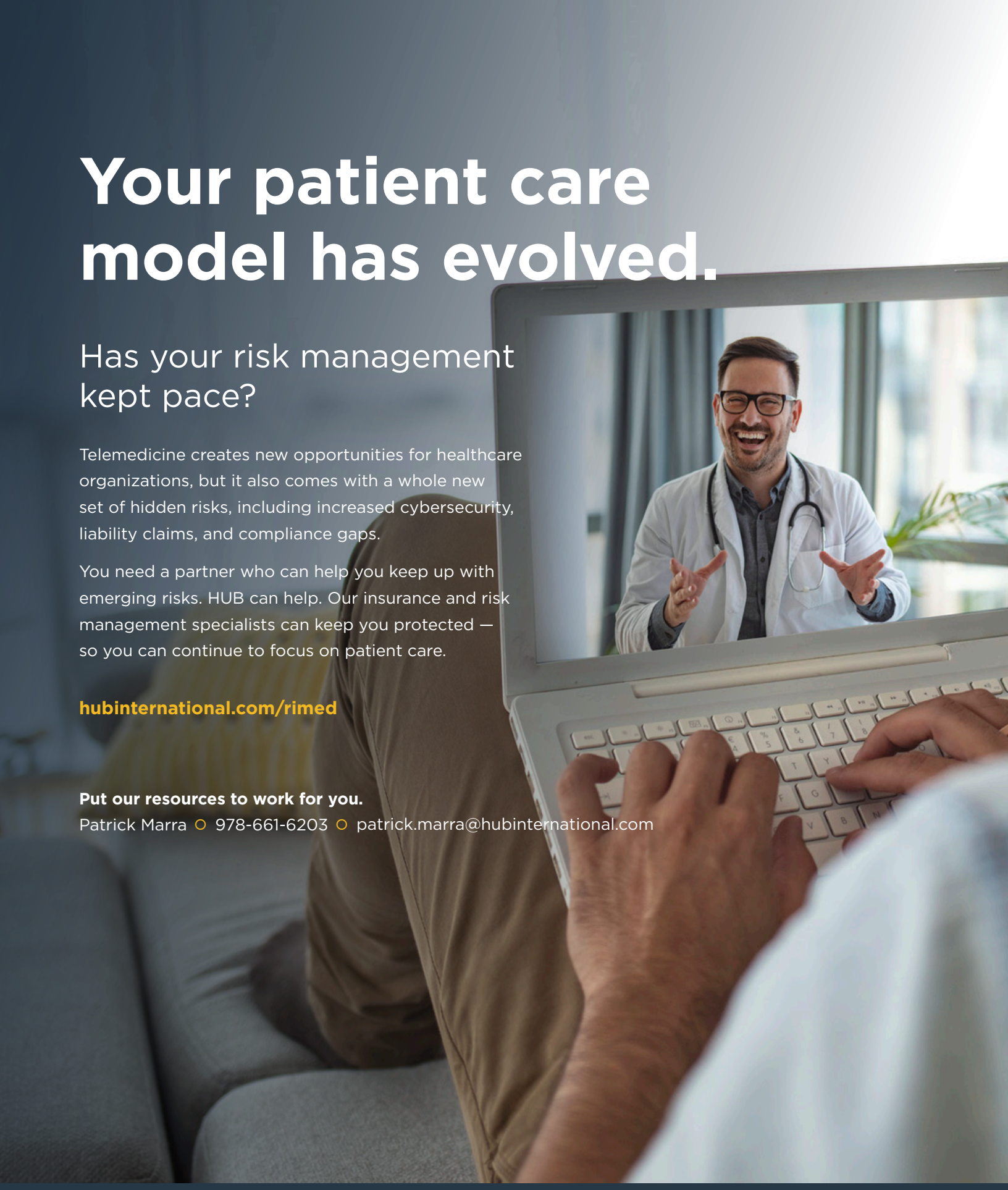

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A Case of Orbital Apex Syndrome as a Complication of Herpes Zoster Ophthalmicus

BRANDON S. KINGREY, MD; ELIZABETH A. CRETARA, MD; WENDY S. CHEN, MD, PhD

ABSTRACT

We present a case of herpes zoster ophthalmicus (HZO) with a rare complication of orbital apex syndrome (OAS) manifesting as optic perineuritis with multiple cranial nerve palsies. A 65-year-old with COPD presented to the hospital with a vesicular rash involving his left eyelid. He was admitted for HZO and a concurrent COPD exacerbation. The HZO was treated with antivirals and the COPD exacerbation was treated with corticosteroids. On hospital day three, he developed left-sided ptosis, ophthalmoplegia, and a mid-dilated fixed pupil. MRI of the brain demonstrated enhancement of the left optic nerve sheath, rectus muscles, and periorbital soft tissues. He was diagnosed with OAS and treated with an increased dose of corticosteroids. After two months, his orbital symptoms resolved. This case is unique because the patient developed HZO in the setting of corticosteroid treatment for a COPD exacerbation, and his HZO progressed to OAS despite proper initiation of antiviral therapy.

KEYWORDS: Herpes Zoster Ophthalmicus, Orbital Apex Syndrome

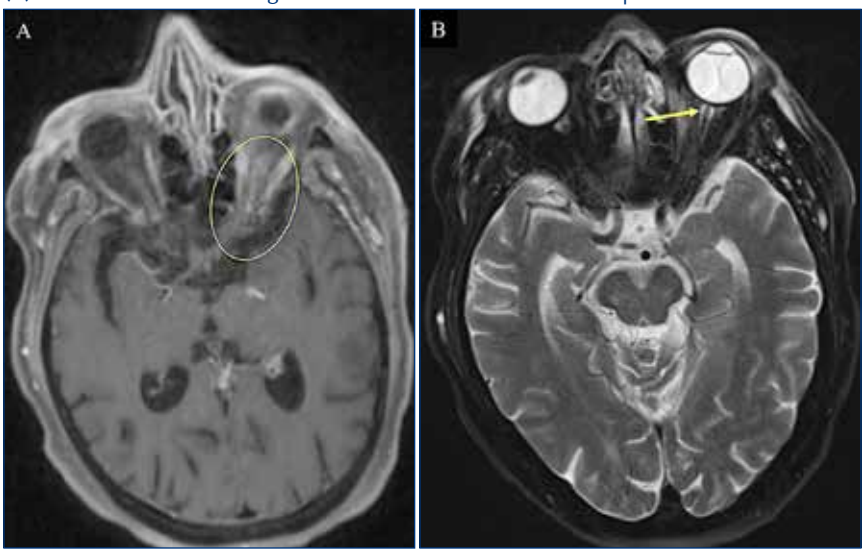
CASE REPORT

A 65-year-old male with chronic obstructive pulmonary disease (COPD) presented to his primary care physician with pain, pruritus, redness, and a watery discharge in his left eye for six days and was diagnosed with conjunctivitis. He concurrently developed a COPD exacerbation which was treated with prednisone 30 mg daily. Four days later, the patient developed a vesicular rash over the left brow and presented to the emergency department of a tertiary hospital center.

Upon initial evaluation by the ophthalmology service, his best corrected visual acuity was 20/25 in the right eye and 20/60 in the left eye. Pupils were equal and reactive without an afferent pupillary defect, and extra-ocular movements were full. The patient had a vesicular rash over the left side of his face including the forehead, eyelid margin, and lateral nose. Slit-lamp biomicroscopy showed diffuse left upper eyelid edema and conjunctival injection with temporal chemosis. There were no pseudodendritic lesions of the cornea, and the dilated fundus exam was normal. He was diagnosed with HZO and started on IV acyclovir 800mg three times daily. On hospital day 2, the prednisone dose was increased to 40 mg for worsening wheezing. On hospital day 3, the ophthalmology service noted a new onset left-sided ptosis, ophthalmoplegia, and a mid-dilated fixed pupil. Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) of the brain with and without contrast demonstrated enhancement of the left optic nerve sheath, pre-septal and post-septal soft tissues, inferior and medial rectus muscles, and periorbital soft tissues (**Figure 1**). The MRA was unremarkable. Oral prednisone was increased to 60 mg and continued at discharge. The patient was transitioned to oral valacyclovir to complete 14 days of antiviral therapy, and he was prescribed Maxitrol ointment for skin and eyelid lesions.

At the outpatient ophthalmology clinic one week later, the patient had persistent ophthalmoplegia and ptosis. Oral

Figure 1. MRI Brain Images Showing Orbital Apex Syndrome.
(**A**) Axial T1 with Gadolinium demonstrating enhancement of the left orbital apex, left optic nerve sheath, pre-septal and post-septal soft tissues, and left-sided rectus muscles.
(**B**) Axial T2 FS demonstrating concentric enhancement of the left optic nerve sheath.



prednisone 60mg was continued for one more week followed by a taper in conjunction with his primary care doctor over one month as his COPD symptoms allowed. At one-month follow-up, the patient had developed neurotrophic keratouveitis OS which was treated with prednisolone acetate drops, ofloxacin drops, and a Prokera lens. At two-month follow-up, the ophthalmoplegia, ptosis, anisocoria, and neurotrophic keratouveitis had resolved, and the Prokera lens was removed. At six-month follow-up, he remained stable off of oral prednisone with a best-corrected visual acuity of 20/50 OS, no ophthalmoplegia or ptosis, and a normal pupil exam.

DISCUSSION

This patient developed HZO in the setting of corticosteroid therapy for a COPD exacerbation. Moreover, he progressed to OAS despite appropriate therapy with IV acyclovir. HZO occurs from reactivation of the varicella zoster virus in the ophthalmic branch of the trigeminal nerve. OAS refers to optic neuropathy and ophthalmoplegia from a disease process affecting the superior orbital fissure and optic canal.[1] This patient's distribution of facial lesions, eyelid edema, and conjunctival injection were clinically diagnostic for HZO. The motility deficits, ptosis, and parasympathetic pupillary dysfunction suggested involvement of the superior and inferior branches of the oculomotor nerve within the superior orbital fissure. The MRI demonstrating concentric optic nerve sheath enhancement suggested pathology within the optic canal. Involvement of both the superior orbital fissure and optic canal was consistent with OAS.

OAS is an uncommon complication of HZO that typically develops days to weeks after the initial vesicular rash.[2,3] Associated symptoms often include proptosis, orbital myositis, and soft tissue inflammation.[1] The most common radiographic findings include enhancement of extraocular muscles, optic nerve sheath, and portions of cranial nerves including tracts and/or nuclei.[4,5] Several studies report interval recovery in these findings after treatment.[5,6] Risk factors for the development of HZO-OAS include age over 50 years, immunocompromise, and failure to receive the herpes zoster vaccine.[6,7] Possible etiologies include spread of the virus to nearby nerves, direct cytopathic effects of the virus, contiguous inflammation, ischemia from vasculitis, demyelination, or a combination of these factors.[7] Although COPD is not commonly recognized as a risk factor for development of HZO, COPD is known to cause a dysregulated immune function and is associated with an increased risk of Herpes Zoster especially when treated with oral corticosteroids.[8] In this case, the corticosteroid treatment for a COPD exacerbation may have allowed reactivation of HZO.

There is no standard treatment for HZO-OAS, and current treatment guidelines are based on expert opinion. Dworkin et al. recommended the use of systemic corticosteroids in patients with HZO complicated by polyneuritis, and many other authors have reported a good treatment response to a combination of steroids and antivirals.[3,6,7,9,10,11] In most cases, steroids are initiated after the antiviral medication to treat the inflammatory response of OAS.[7] Prognosis is generally good with significant improvement in visual acuity and ophthalmoplegia in most patients.[2,3] Resolution of symptoms has been reported as early as two weeks and as late as 1.5 years with an average time to recovery of 2–4 months from symptom onset.[2,3] This case is unique because the patient was already taking oral corticosteroids for a COPD exacerbation concurrent to developing HZO-OAS. Despite initial worsening of the HZO-OAS on steroid therapy, discontinuation of steroid was not needed for subsequent clinical improvement.

The role of corticosteroids in reactivation of herpes zoster and subsequent role in treating the infection-associated inflammation is unclear. Further studies should examine the effect of systemic corticosteroids on incidence, symptom severity, and recovery of orbital apex syndrome in patients with HZO.

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Authors

Brandon S. Kingrey, MD, Warren Alpert Medical School of Brown University, Providence, Rhode Island

Elizabeth A. Cretara, MD, Resident 2019, Ophthalmology Division of The Warren Alpert Medical School of Brown University, Providence, Rhode Island; UNM Health Sciences Center, University of New Mexico, Albuquerque, NM

Wendy S. Chen, MD, PhD, Ophthalmology Division of The Warren Alpert Medical School of Brown University, Providence, Rhode Island

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Correspondence

Brandon S. Kingrey, MD
15525 Park Lake Rd
Edmond, OK 73013
Brandon_Kingrey@alumni.brown.edu

IgA Vasculitis With Concurrent ANCA-Positivity in the Setting of Bacterial Endocarditis

MICHELLE XIONG, BS; HANNAH SINGER, MD; EDWARD BAE, MD; REGINE MATHIEU, MD; SU-JEAN SEO, MD; CATHY M. MASSOUD, MD

ABSTRACT

Cutaneous small vessel vasculitis (CSVV) or leukocytoclastic vasculitis (LCV) is a group of immune complex mediated vasculitides that affect dermal capillaries or post-capillary venules and classically presents as lower extremity palpable purpura. CSVV can be subdivided by antibody type and clinical features. In patients presenting with signs of LCV and ANCA positivity, clinicopathologic correlation is important in characterizing the type of vasculitis.

We report an uncommon case of IgA vasculitis with concurrent ANCA-positivity attributed to bacterial endocarditis.

KEYWORDS: IgA vasculitis, ANCA, endocarditis

INTRODUCTION

Cutaneous small vessel vasculitis (CSVV) or leukocytoclastic vasculitis (LCV) is a group of immune complex mediated vasculitides that affect dermal capillaries or post-capillary venules and classically presents as lower extremity palpable purpura. CSVV may be subdivided according to antibody type and clinical features. Recognized CSVV variants include IgA vasculitis (Henoch-Schönlein purpura) and urticarial vasculitis.[1] Medium vessel vasculitis may also involve small vessels of the skin, and therefore can morphologically overlap with CSVV. Medium vessel vasculitides are classified into two broad categories according to anti-neutrophil cytoplasmic antibody (ANCA) association. Vasculitides with ANCA positivity include microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. ANCA-negative vasculitides typically include entities such as polyarteritis nodosa and cryoglobulinemic vasculitis. However, ANCA positivity alone is non-specific and may arise independent of vasculitis in the setting of other autoimmune disorders, infections, or medications. Clinicopathologic correlation is essential to navigate the potential for morphologic overlap between cutaneous small and medium vessel vasculitis as well as to accurately interpret ANCA status. Here, we report an uncommon case of a patient with biopsy-proven cutaneous IgA vasculitis and concurrent ANCA-positivity in the setting of bacterial endocarditis.

CASE REPORT

A 52-year-old Caucasian man with a history of intravenous drug use, hypertension, hepatitis B virus, and hepatitis C virus presented with shortness of breath, bilateral lower extremity edema with concurrent cutaneous eruption (**Figure 1**). He was diagnosed with enterococcus endocarditis by blood cultures and echocardiogram; he was initially managed with intravenous ampicillin and ceftriaxone. Urine toxicology screen was positive for cocaine, fentanyl, and methadone. His hospital course was complicated by acute kidney injury, and a broad workup for worsening kidney function revealed a positive p-ANCA (1:1280, ref range <1:20) and myeloperoxidase antibody (MPO Ab) (3.2, ref range 0-0.9). c-ANCA; C3 and C4 levels were negative or within normal limits. Initial urinalysis demonstrated granular casts, few erythrocytes with normal morphology, and proteinuria. His renal function was attributed to acute tubular necrosis in the setting of cardiogenic or septic shock and improved within a few days. Ten days after the patient was admitted, dermatology was consulted to evaluate for possible vasculitis.

Physical examination revealed purpuric papules of bilateral ankles and dorsal feet (**Figure 2**) suspicious for LCV. The distribution sparing fingertips, volar

Figure 1. Purpuric papules of the left ankle on admission.

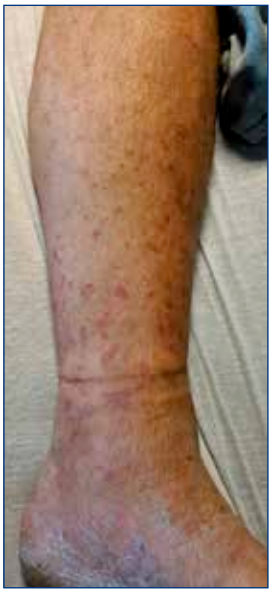


Figure 2. Purpuric papules of the left dorsal foot on day 10 of admission and initial dermatology consultation.

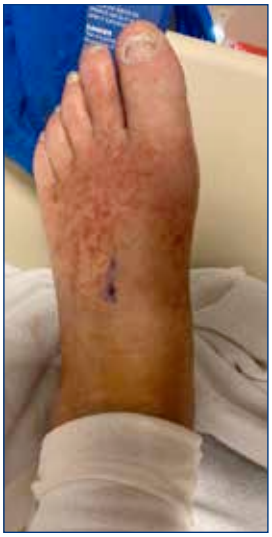


Figure 3. Circular purpura of the thigh.

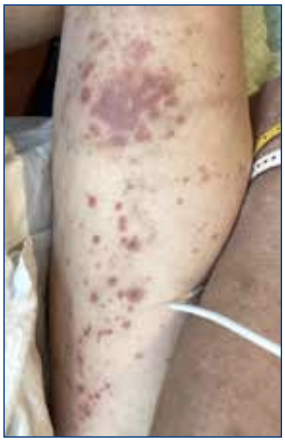
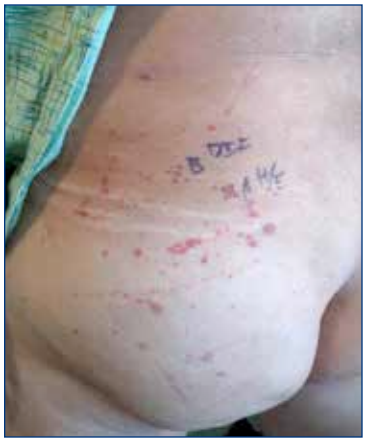


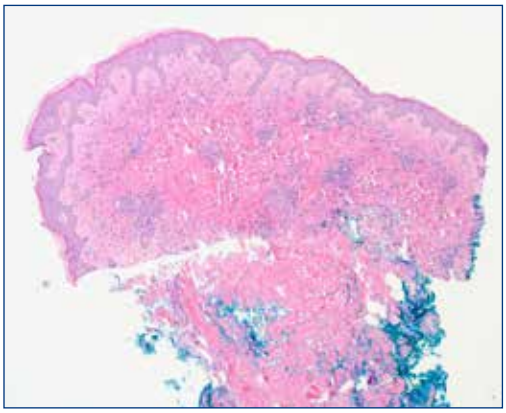
Figure 4. Purpuric papules of the lower back

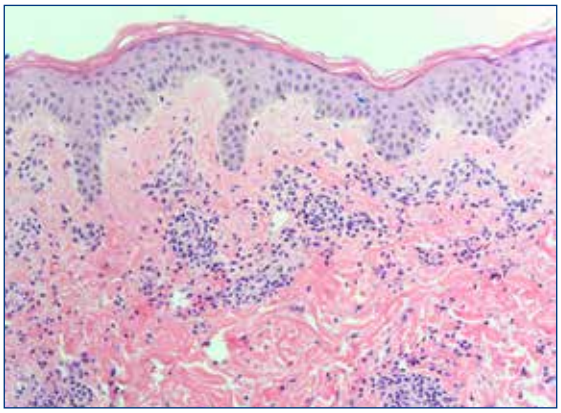


toes, and ears decreased suspicion of levamisole-induced purpura and septic emboli.

Five days after initial dermatology consultation, the patient developed new petechiae and palpable purpura of the proximal lower extremities that extended to the buttocks and lower lateral lumbar back (**Figures 3,4**). Punch biopsies of the new eruption on the left lower back were performed. Pathology revealed neutrophil karyorrhexis, perivascular fibrin deposition, and extravasated erythrocytes involving dermal capillaries and post-capillary venules, diagnostic of LCV (**Figures 5,6).** Direct immunofluorescence studies (DIF) were significant for IgA perivascular granular positivity, IgM and C3 granular perivascular positivity, and shaggy perivascular fibrinogen deposition. Together, the findings were diagnostic of IgA vasculitis. The patient continued systemic antimicrobials for known enterococcus endocarditis and underwent surgical management with aortic and mitral valve replacement. His cutaneous lesions, renal function, and overall health improved.

Figures 5, 6. Histopathologic findings from punch biopsy of the lower back (H&E, original magnification x4 and x20). Neutrophil karyorrhexis, early perivascular fibrin deposition, and extravasated erythrocytes involving dermal capillaries and post-capillary venules were seen.





DISCUSSION

IgA vasculitis or Henoch-Schönlein purpura is a CSVV mediated by IgA immune complex deposition. It is most often seen in children and presents with a tetrad of clinical manifestations: palpable purpura, arthritis, abdominal pain, and renal involvement. IgA vasculitis is less common in adults yet portends an increased risk for renal involvement.[2,3] Diagnosis is based upon clinicopathological correlation, including skin and or renal biopsies with DIF. A wide range of causative factors have been associated with IgA vasculitis including infections (such as upper respiratory infections and endocarditis), medications, inflammatory bowel disease, systemic lupus erythematous, and genetic polymorphisms.[4,5]

ANCA-positivity is most commonly associated with granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. ANCA-positivity has also been reported in many other clinical scenarios: medication-associated, autoimmune disorders, levamisole-induced vasculopathy, and bacterial or viral infections. Exogenous triggers such as medications can induce ANCA-positivity which can concomitantly present with vasculitis. The most commonly reported drug to induce ANCA vasculitis is propylthiouracil. Other reported agents include: methimazole, hydralazine, TNF-alpha inhibitors, minocycline, clozapine, allopurinol, D-penicillamine, phenytoin, levamisole, and sulfasalazine.[6-8] Drug-induced ANCA vasculitides are typically characterized by anti-MPO antibodies (p-ANCA pattern), yet anti-PR3 antibodies (c-ANCA pattern) are possible and the presence of multiple antibodies raises suspicion for drug-induced ANCA vasculitis.[8] In addition to systemic vasculitides, patients with connective tissue disorders such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and inflammatory myositis can show ANCA positivity.[9] Autoimmune gastrointestinal conditions such as ulcerative colitis, primary sclerosing cholangitis, and autoimmune hepatitis also often present with positive ANCAs, but without clear clinical significance.[10-12]

For our patient, in the setting of cocaine use and enterococcus endocarditis, it is especially important to recognize that both of these clinical factors can lead to ANCA positivity. About 70% of cocaine in the United States is contaminated with levamisole which has been documented in numerous

reports of ANCA-positive vaculitis.[13,14] In these cases, patients commonly present with arthralgias, widespread retiform purpura involving the face, ears, trunk, and extremities, and histopathologic findings of occlusive thrombotic vasculopathy with LCV.[15] ANCA labs typically demonstrate both cytoplasmic and perinuclear reactivity and positive ELISA.[14]

ANCA positivity can often be seen in the setting of infective endocarditis (IE). One case series reported that 24% of patients with IE had positive ANCA, and were more likely to have renal impairment.[16] Notably, ANCA-positive IE can mimic ANCA-positive LCV with non-specific systemic signs, yet patients with ANCA-positive IE were less likely to have pulmonary and articular signs.[16] The proposed mechanisms linking infections and ANCA positivity include autoantigen complementarity, molecular mimicry, epigenetics, neutrophil extracellular traps activation and release (NETosis), and toll-like receptors.[17] In autoantigen complementarity, it is thought that a protein complementary to the autoantigen elicits an immune response.[18–20] The molecular mimicry theory suggests that the cross reactivity between antibodies to pathogens and self-antigens lead to autoimmune disease. An example of this phenomenon can be seen with LAMP-2, a neutrophil vesicle surface membrane protein that contains MPO and PR3. Evidence suggests that this protein cross reacts with a bacterial fimbrial protein found on Gram-negative bacteria, like *Escherichia coli, Klebsiella pneumonia,* and *Proteus mirabilis*.[21] Consequently, autoantibodies to LAMP-2 develop in response to an infection with fimbrial proteins produced by these pathogens.[22,23] Epigenetics proposes that environmental factors, such as an infection, influence expression of DNA sequences.[24,25] NETosis is a specific type of neutrophil-related cell death which releases MPO and PR3; this event can lead to the development and sustained production of ANCA antibodies.[26–28] Bacteria, including *Enterococcus, Staphylococcus, and Streptococcus,* are pathogens that can induce neutrophil-related cell death.[28] The mechanism of toll-like receptors and ANCA formation involves the interaction of pathogen microorganism components with toll-like receptors; a study demonstrated production of ANCA antibodies in vitro from a toll-like receptor ligand.[29]

ANCA-positivity in the setting of IgA vasculitis is uncommon and the clinical significance is unclear. In some studies, patients with ANCA-positive IgA nephropathy demonstrated a higher frequency of systemic and pulmonary symptoms versus ANCA-negative IgA nephropathy patients.[30,31] Kim et al reported increased pulmonary and neurological symptoms in ANCA-positive IgA vasculitis compared to ANCA-negative cases. Renal injury prognosis, however, did not correlate with ANCA status in patients with IgA vasculitis.[32] The coexistence of ANCA positivity and IgA vasculitis may represent an overlap syndrome–ANCA positivity may reflect an inflammatory reaction of IgA vasculitis resulting in pulmonary and neurologic manifestations – or the coexistence may be coincidental.[32,33]

Our patient's presentation of IgA vasculitis is most likely attributable to bacterial endocarditis, as his vasculitis improved with treatment of IE. The ANCA positivity discovered during his acute kidney injury workup may have represented NETosis from *Enterococcus* infection. Despite recent cocaine use, the cutaneous morphology and histopathology were not consistent with levamisole-induced vasculopathy, though it is unclear if this may have contributed to ANCA-positivity. Thus, our patient's coexistent IgA vasculitis and ANCA positivity were felt to be coincidental, in the setting of IE.

CONCLUSION

In patients presenting with signs of LCV and ANCA positivity, clinicopathologic correlation is paramount in characterizing the type of vasculitis. Additionally, clinicians should recognize the many potential causes of ANCA positivity, including infections, medications, autoimmune gastrointestinal diseases, and non-vasculitic autoimmune diseases.

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Authors

Michelle Xiong, BS, Warren Alpert Medical School of Brown University, Providence, RI.

Hannah Singer, MD, Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, RI.

Edward Bae, MD, Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, RI.

Regine Mathieu, MD, Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, RI.

Su-Jean Seo, MD, Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, RI.

Cathy M. Massoud, MD, Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, RI.

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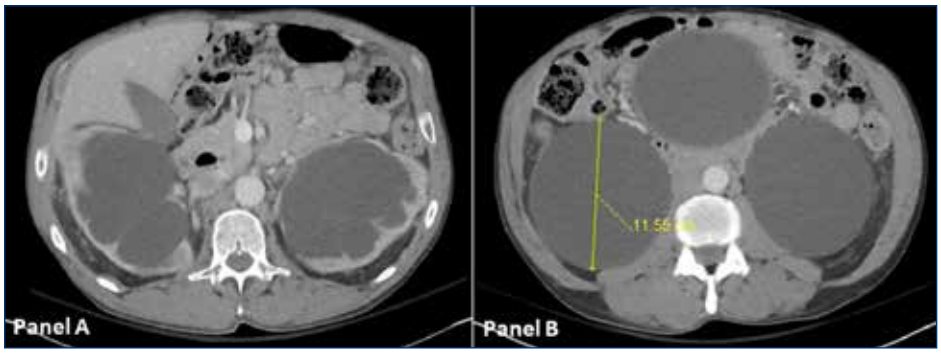
Correspondence

Michelle Xiong
Brown University
Box G-9552
Providence, RI 02912
Michelle_xiong@brown.edu

Severe Bilateral Hydroureteronephrosis Due to Chronic Obstructive Uropathy

BASMA MERHI, MD

Panel A, B. Computed tomography of abdomen and pelvis with contrast showed severe bilateral hydroureteronephrosis with bilateral cortical thinning and distended bladder due to enlarged prostate.



A 58-year-old male patient with no known past medical history since he had no prior regular medical care presented after a motor vehicle accident during which he lost consciousness while driving. He reported suprapubic fullness, increased urinary frequency and hesitancy over the last 2 years. He denied any decrease in his appetite, weight loss or lower extremity swelling. Physical exam was significant for mild abdominal distention and enlarged prostate on digital rectal exam. Labs showed blood urea nitrogen at 234 mg/dL (normal 6–25 mg/dL) and serum creatinine 16 mg/dL (0.64–1.27 mg/dL). Urinalysis revealed 3+ blood, no protein and no leukocytosis. Urine sediment was bland. Computed tomography of abdomen and pelvis with contrast showed severe bilateral hydroureteronephrosis with bilateral cortical thinning and distended bladder due to enlarged prostate (**Panel A,B**). Foley catheter was placed and drained 7.2 liters of urine over the next few hours. Due to the chronicity of the obstructive uropathy, patient required intermittent hemodialysis due to decreased solute clearance and continued dialysis dependent due to nonrecovery kidney function. He was started on tamsulosin 0.4 mg daily and oxybutynin 5mg twice a day. He remained dialysis dependent with chronic Foley catheter upon his discharge with outpatient urology follow-up. Panel A shows cortical thinning bilaterally with distended renal collecting systems. **Panel B** shows ureteral distention, 11.5 cm in diameter (upper limit of normal 3 mm).[1]

In a study of 2,127 patients who presented with obstructive uropathy, 1,638 underwent percutaneous nephrostomy tube placement. Of those, 1,313 (78%) presented initially with acute kidney injury; 746 recovered function within 7 days after PCN; 216 patients required temporary dialysis; 45 patients progressed to end stage kidney disease (ESKD). Underlying chronic kidney disease was a significant risk factor for AKI from obstruction, while CKD and advanced stage of AKI were significant risk factors for progression to ESKD.[2]

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Author

Basma Merhi, MD, Assistant Professor of Medicine, Clinical Educator, Division of Kidney Disease and Hypertension, Warren Alpert Medical School of Brown University.

Correspondence

bmerhi@Lifespan.org

Increased Prevalence of Alcohol-Related Gastrointestinal and Liver Diseases During the COVID-19 Pandemic

SAVAN KOTHADIA, MD; WAIHONG CHUNG, MD; MAY MIN, MD; FIRRAH SAEED, MD; JAMES SCHARFEN, MD; FADLALLAH HABR, MD

ABSTRACT

BACKGROUND: Higher prevalence of alcohol-related gastrointestinal (GI) and liver diseases (ARGLDs) were anecdotally reported during the COVID-19 pandemic, but little published evidence exists.

METHODS: A healthcare system audit of inpatient GI consults was performed during the pandemic's lockdown phase (3/23/2020–5/10/2020, n=558) and reopening phase (6/1/2020–7/19/2020, n=711) with comparison to those timeframes in 2019.

RESULTS: Consult volume decreased by 27.7% during the lockdown, but the proportion of ARGLDs increased by 59.6% (p=0.03). This trend continued during reopening, with potentially more severe disease as more patients required endoscopic intervention. Patients with alcoholic hepatitis during reopening were younger compared to the lockdown.

CONCLUSIONS: Our study demonstrates increased prevalence and severity of ARGLDs amongst younger individuals during the COVID-19 pandemic. This increase started during the lockdown but worsened despite relaxation of restrictions. Systems to increase screening for and treatment of alcohol use disorder as society recovers from the pandemic remain imperative.

KEYWORDS: Alcohol Use Disorder, Alcoholic Hepatitis, Alcoholic Cirrhosis, Alcoholic Pancreatitis, Alcohol-related Liver Disease

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on public health with high rates of infection, hospitalization, morbidity, and mortality seen throughout the world.[1-3] In addition to infection-related consequences, the pandemic has also had important implications for individuals with non-communicable diseases (NCDs). Lockdowns, overwhelmed medical systems, and public fear contributed to delays in care as well as deferred diagnostic and therapeutic procedures for NCDs.[4-7] Experts had warned that medical services for patients with chronic NCDs, including cirrhosis or malignancy, had been hampered due to the pandemic.[5,8]

Patients with chronic NCDs requiring frequent healthcare utilization are at increased risk for adverse outcomes related to disruptions in their care. Individuals with substance use disorders, in particular alcohol use disorder, have been identified as one such vulnerable population.[9] Psychosocial stressors including grief, social isolation, and economic hardship were all heightened during the pandemic and are known risk factors for anxiety, depression, and substance use disorders.[8,10] Furthermore, pandemic restrictions had interrupted our primary avenues for treating alcohol use disorder, which typically involve multidisciplinary medical providers, organized support groups, and interpersonal support networks. A 2021 study showed that while 81% of individuals who met the criteria for alcohol use disorder had received medical care during the previous year, 12% had been counseled to reduce their alcohol use and only 6% actually received treatment.[11] Preliminary studies showed increased alcohol consumption during the pandemic related to stress, job loss, and lockdowns.[12-14] Though anecdotal reports have suggested that increased alcohol consumption had led to an increase in alcohol-related gastrointestinal (GI) or liver diseases (ARGLDs), limited published data is available to support these observations. A recent micro-simulated model suggested that the short-term increase in alcohol consumption during the COVID-19 pandemic will lead to potentially 8000 alcoholic-liver disease-related deaths and thousands more cases of alcohol-related liver disease through 2040 in the United States.[15] There has been recent evidence of the pandemic's effect on the increased prevalence of general alcohol use disorder and the role for universal alcohol screening tools such as AUDIT-C.[16]

To objectively quantify the immediate and delayed impact of the COVID-19 pandemic on the prevalence of various GI and liver diseases, and to carefully identify any gaps in the provision of gastroenterology care under the infection control guidelines during the pandemic, we conducted a system-wide audit of adult inpatient gastroenterology services within our hospital system and analyzed our caseload during the pandemic against that of historical records. It is hypothesized that hospitalization for certain chronic GI and liver diseases and the incidence of ARGLDs would be affected by the COVID-19 pandemic.

MATERIALS AND METHODS

Study Design

This study was designed as a retrospective cohort analysis in the form of a hospital system-wide audit. The study cohort consisted of consecutive adult (≥18 years of age at the time of presentation) subjects, who were evaluated by the inpatient gastroenterology consult services at three hospitals in the Lifespan health system in Rhode Island during the study period.

The COVID-19 pandemic was broken down into the lockdown phase, defined as March 23, 2020 (the start date of the government's stay-at-home order) to May 10, 2020 (the end date of the stay-at-home order), and the reopening phase, defined as June 1, 2020 (the start date of the government's Phase 2 reopening plan) to July 19, 2020. This breakdown serves as a means to assess the immediate and delayed impact of the pandemic. To account for seasonal variations in the pattern of hospital admissions, two corresponding timeframes from 2019 were used as controls: the lockdown-reference phase was defined as March 25, 2019 to May 12, 2019, and the reopening-reference phase was defined as June 3, 2019 to July 21, 2019.

Subjects were identified by querying the electronic medical record system, Epic (Epic Systems, Madison, WI), for the presence of a gastroenterology consult note in the patient's chart during the study period. The study was conducted in compliance with the Declaration of Helsinki and its design was approved by the institutional review board at our hospital system.

Data Extraction

The primary GI diagnosis for each gastroenterology consult as documented by the consulting physician was extracted from the consult note and mapped to an International Classification of Diseases (ICD)-9 based diagnosis. Consults were allowed to be associated with more than one diagnosis if they were documented separately by the consulting physician. Endoscopic data was obtained by querying the endoscopy reporting software, ProVation MD (ProVation Medical, Minneapolis, MN) using the patient's medical record number. Laboratory tests performed on the day of presentation were extracted from the chart's electronic medical record for analysis. Missing laboratory results were imputed using the k-nearest neighbor algorithm.[17]

Statistical Methods

Categorical variables were reported as numerator and percentage and compared using the Chi-square test. Normally distributed continuous variables were reported as mean and standard deviation and compared using the t-test. Non-normally distributed continuous variables were reported as median and interquartile range and compared using the Mann-Whitney U test. A p-value of <0.05 was considered statistically significant.

RESULTS

Overall GI Consults

As shown in **Table 1**, the overall volume of inpatient GI consults decreased by 27.7% during the lockdown phase (n = 558, compared to lockdown-reference phase = 772), but the volume was restored to 100% during the reopening phase (n = 711, compared to reopening-reference phase = 711). There were no significant differences between the two pandemic phases and the two reference phases with regards to patient demographics (age, gender, ethnicity, and preferred language), length-of-stay, or discharge dispositions.

The proportion of GI consults that required inpatient endoscopy was significantly lower during the lockdown phase (36.20% vs. 42.49%, p = 0.02), likely as a consequence of a severely reduced endoscopy capacity due to personal protective equipment shortages and infection control restrictions at the beginning of the pandemic. As the endoscopy units resumed normal operating capacity during the reopening phase, the proportion of GI consults that were associated with inpatient endoscopy also returned to historical levels. The proportion of GI consults requiring emergent endoscopy performed in the emergency room was not affected by the COVID-19 pandemic.

Distributions of GI Diagnoses

Table 2 shows the distribution of selected groups of GI diagnoses associated with inpatient GI consults received during the two pandemic phases compared to the two reference phases. The proportion of GI consults for overt GI bleeding (hematemesis, hematochezia, or melena), which accounted for the majority of inpatient consults, did not change during the lockdown phase or the reopening phase. Similarly, the distributions of consults amongst acute non-alcoholic liver diseases (drug-induced liver injury, viral hepatitis, ischemic hepatitis, immune-mediated hepatitis, autoimmune hepatitis, congestive hepatopathy, acetaminophen toxicity, or acute fatty liver of pregnancy), biliary obstruction/injury (choledocholithiasis, ascending cholangitis, primary sclerosing cholangitis, biliary strictures, or bile leak), cirrhosis management (management of symptomatic ascites, hepatic encephalopathy, variceal bleeding, hepatic hydrothorax, hepatorenal syndrome, or spontaneous bacterial peritonitis in patients with known cirrhosis), and percutaneous endoscopic gastrostomy (PEG) placement were not significantly different between the lockdown phase and the lockdown-reference phase.

In contrast, the relative volume of inpatient GI consults for ARGLDs (alcoholic hepatitis, acute decompensation in patients with known alcoholic cirrhosis, alcoholic pancreatitis, or alcoholic gastritis) increased by 59.6% (8.06% vs. 5.05%, p = 0.03), while that for functional GI disorders (irritable bowel syndrome, functional dyspepsia, functional abdominal bloating, functional constipation/diarrhea, or functional nausea/vomiting) and *Clostridium difficile* (*C. diff*)

Table 1. Patient Demographics and Clinical Characteristics of All Inpatient Gastroenterology Consults during the Lockdown, Lockdown-Reference, Reopening, and Reopening-Reference Phases

	Lockdown	Lockdown Ref.	P-value	Reopening	Reopening Ref.	P-value
Total (no.)	**558**	**772**		**711**	**711**	
Age (years, SD)	63.00 (18.51)	63.09 (18.58)	0.94	63.31 (18.33)	62.35 (19.75)	0.35
Male (no.)	279 (50.00%)	366 (47.41%)	0.39	330 (46.41%)	345 (48.52%)	0.43
Ethnicity (no.)						
Caucasian	441 (79.03%)	594 (76.94%)	0.37	575 (80.87%)	555 (78.06%)	0.19
Black	56 (10.04%)	71 (9.20%)	0.61	48 (6.75%)	63 (8.86%)	0.14
Hispanic	50 (8.96%)	84 (10.88%)	0.25	71 (9.99%)	70 (9.85%)	0.93
Asian	7 (1.25%)	13 (1.68%)	0.53	10 (1.41%)	11 (1.55%)	0.83
Others	4 (0.72%)	10 (1.30%)	0.31	7 (0.98%)	11 (1.55%)	0.34
Pref. Language (no.)						
English	495 (88.71%)	669 (86.66%)	0.26	632 (88.89%)	614 (86.36%)	0.15
Spanish	37 (6.63%)	63 (8.16%)	0.30	58 (8.16%)	58 (8.16%)	1.00
Others	26 (4.66%)	36 (4.66%)	1.00	21 (2.95%)	33 (4.64%)	0.10
Discharge Disposition (no.)						
Home	441 (73.66%)	563 (72.93%)	0.77	547 (76.93%)	546 (76.79%)	0.95
Expired	23 (4.12%)	23 (2.98%)	0.26	22 (3.09%)	24 (3.38%)	0.76
Length of Stay (days, SD)	6.28 (7.63)	6.05 (6.71)	0.57	6.24 (7.88)	5.72 (5.81)	0.16
Endoscopy (no.)						
Inpatient	202 (36.20%)	328 (42.49%)	0.02	318 (44.73%)	317 (44.59%)	0.96
Emergent	28 (5.02%)	42 (5.44%)	0.73	37 (5.20%)	55 (7.74%)	0.05

Table 2. Distribution of Selected Groups of GI Diagnoses during the Lockdown, Lockdown-Reference, Reopening, and Reopening-Reference Phases

	Lockdown (%)	Lockdown Ref. (%)	P-value	Reopening (%)	Reopening Ref. (%)	P-value
Total	**558**	**772**		**711**	**711**	
Gastrointestinal Bleeding	177 (31.72%)	255 (33.03%)	0.61	196 (27.57%)	225 (31.65%)	0.09
Non-Alcoholic Liver Diseases	53 (9.50%)	71 (9.20%)	0.85	56 (7.88%)	41 (5.77%)	0.11
Alcoholic GI/Liver Diseases	45 (8.06%)	39 (5.05%)	0.03	50 (7.03%)	29 (4.08%)	0.02
Biliary Obstruction/Injury	42 (7.53%)	64 (8.29%)	0.61	67 (9.42%)	65 (9.14%)	0.85
Cirrhosis Management	33 (5.91%)	52 (6.74%)	0.55	54 (7.59%)	34 (4.78%)	0.03
Inflammatory Bowel Diseases	32 (5.73%)	29 (3.76%)	0.09	52 (7.31%)	46 (6.47%)	0.53
PEG Placement	17 (3.05%)	25 (3.24%)	0.84	42 (5.91%)	33 (4.64%)	0.29
Functional Disorders	13 (2.33%)	62 (8.03%)	<0.01	24 (3.38%)	16 (2.25%)	0.20
Clostridioides difficile Infection	1 (0.18%)	11 (1.42%)	0.02	12 (1.69%)	15 (2.11%)	0.56

infection decreased by 71.0% (2.33% vs. 8.03%, $p < 0.01$) and 87.3% (0.18% vs. 1.42%, $p = 0.02$), respectively, during the lockdown phase compared to the lockdown-reference phase. There was also a trend toward more inflammatory bowel diseases (5.73% vs. 3.76%), but the difference was not statistically significant ($p = 0.09$).

The distribution of GI consults amongst overt GI bleeding, acute non-alcoholic liver diseases, biliary obstruction/injury, inflammatory bowel diseases, PEG placement, and *C. diff* infection were not significantly different between the reopening phase and the reopening-reference phase. The proportion of consults for ARGLDs, however, remained elevated by 72.5% (7.03% vs. 4.08%, $p = 0.02$) during the reopening phase compared to the 2019 reopening-reference phase. The relative volume of consults for cirrhosis management also increased by 58.8% (7.59% vs. 4.78%).

Alcohol-Related GI and Liver Diseases

Patient demographics and clinical characteristics of those GI consults for ARGLDs are shown in **Table 3**. There were no significant differences with regard to age, gender, ethnicity, language preference, length-of-stay, discharge dispositions,

Table 3. Patient Demographics and Clinical Characteristics of Consults for Alcohol-related Gastrointestinal and Liver Diseases during the Lockdown, Lockdown-Reference, Reopening, and Reopening-Reference Phases

	Lockdown	Lockdown Ref.	P-value	Reopening	Reopening Ref.	P-value
Total (no.)	**45**	**39**		**50**	**29**	
Age (years, SD)	56.00 (16.50)	53.00 (12.00)	0.17	51.00 (22.00)	50.00 (17.00)	0.82
Male (no.)	32 (71.11%)	27 (69.23%)	0.85	34 (68.00%)	20 (68.97%)	0.93
Ethnicity (no.)						
Caucasian	31 (68.89%)	26 (66.67%)	0.83	39 (78.00%)	19 (65.52%)	0.23
Black	7 (15.56%)	9 (23.08%)	0.38	5 (10.00%)	2 (6.90%)	0.64
Hispanic	6 (13.33%)	4 (10.26%)	0.66	5 (10.00%)	8 (27.59%)	0.04
Asian	1 (2.22%)	0 (0.00%)	0.35	1 (2.00%)	0 (0.00%)	0.44
Pref. Language (no.)						
English	39 (86.67%)	33 (84.62%)	0.79	44 (88.00%)	26 (89.66%)	0.82
Spanish	3 (6.67%)	4 (10.26%)	0.55	6 (12.00%)	3 (10.34%)	0.82
Discharge Disposition (no.)						
Home	30 (66.67%)	28 (71.79%)	0.61	43 (86.00%)	21 (72.41%)	0.14
Expired	2 (4.44%)	1 (2.56%)	0.64	2 (4.00%)	2 (6.90%)	0.57
Length of Stay (days, SD)	6.00 (6.00)	5.00 (7.00)	0.66	5.00 (5.00)	6.00 (6.00)	0.42
Endoscopy (no.)						
Inpatient	7 (15.56%)	9 (23.08%)	0.38	17 (34.00%)	4 (13.79%)	0.05
Emergent	1 (2.22%)	1 (2.56%)	0.92	2 (4.00%)	0 (0.00%)	0.28

or the proportion of consults that required inpatient or emergent endoscopy between the lockdown phase and the lockdown-reference phase. The requirement for inpatient or emergent endoscopy, however, was significantly higher (36.00% vs. 13.79%, p = 0.03) during the reopening phase compared to the reopening-reference phase. This also coincided with a higher proportion of patients that simultaneously presented with both GI bleeding and ARGLDs (10.00% vs. 3.45%, p = 0.29) as well as marginally decreased median hemoglobin (12.01 vs. 13.00, p = 0.29) and elevated median bilirubin (5.00 vs. 2.40, p = 0.32). The proportion of Hispanic patients was also significantly lower (10.00% vs. 27.59%, p = 0.04) during the reopening phase.

When comparing patients diagnosed with ARGLDs admission patterns, some differences were seen between the different study phases. The majority of admissions clustered around the second half of the study period during the lockdown phase, while admissions occurred more regularly throughout the lockdown-reference, reopening, and reopening-reference phases.

Acute alcoholic hepatitis accounts for the majority of the ARGLDs diagnosed during both the lockdown (68.89%) and reopening phases (80.00%). Compared to the reference phases, the relative volume of acute alcoholic hepatitis was marginally higher during the lockdown phase (5.56% vs. 3.63%, p = 0.09), but was significantly higher during the reopening phase (5.63% vs. 2.53%, p = <0.01).

It is worth noting that patients diagnosed with acute alcoholic hepatitis during the reopening phase were significantly younger on average than those during the lockdown phase (51 vs. 56, p = 0.05). This age difference was not detected when comparing the reopening-reference and lockdown-reference phases (55 vs. 55, p = 0.94).

DISCUSSION

While COVID-19 infection and mortality rates have decreased in many regions due to social-distancing, improved testing capability, and vaccination, the "collateral damage" of the pandemic resulting from delayed medical care, increased use of telemedicine, and psychosocial distress are yet to be fully appreciated.[7, 18-20]

Our results demonstrate that during the lockdown phase of the pandemic, the volume of inpatient GI consults decreased by more than a quarter. This can likely be attributed to reduced hospital capacity for non-COVID-19 patients in response to the surge in COVID-19 cases, as well as patients' reluctance to present to the hospital for non-life-threatening illnesses in fear of exposure to the virus. The latter notion is supported by the observation that the proportion of inpatient GI consults for functional disorders decreased drastically during that time. As expected, our results also demonstrated a substantial reduction in the volume of *C. diff* infection. This finding coincides with maximum infection control precautions as well as the suspension of most in-person outpatient services, and thus supports the

internal validity of our findings. Patients of all ethnic backgrounds and language preferences were affected equally by the lockdown.

One of the most salient findings was the significant increase in inpatient ARGLDs, which correlates with data showing increased alcohol consumption during the pandemic.[13,14] We found that there was a 60% increase in the relative volume of inpatient consults for ARGLDs during the lockdown phase with an alarming increase to 72% during the reopening phase compared to the equivalent pre-pandemic timeframes in 2019. Acute alcoholic hepatitis is the most common diagnosis amongst these patients, and its incidence increased most dramatically to more than double during the reopening phase compared to the prior year. In contrast, the proportion of inpatient consults for acute non-alcoholic liver diseases and biliary obstruction/injury, whose disease processes are not known to be affected by COVID-19, remained relatively stable during both the lockdown and reopening phases.

In addition to more patients presenting with ARGLDs since the start of the pandemic, our results also implicate that the disease severity might have been worse. This is exemplified by a nearly three-fold increase in the need for endoscopic intervention as well as concurrent GI bleeding amongst these patients during the reopening phase. The proportion of patients with ARGLDs that underwent endoscopy was not significantly lower during the lockdown period as compared with 2019, despite overall endoscopy volume being severely reduced. This finding indicates that the need for endoscopic intervention was also higher during the lockdown phase. We also discovered that the majority of hospital admissions for ARGLDs during the lockdown occurred around the latter half of that study period, implying that the start of the lockdown phase may have been a trigger for increased alcohol consumption for patients.

A 2020 report suggested that a large proportion of individuals who delayed care were from disenfranchised populations.[7] It is interesting to note that compared to the overall ethnic distribution of all GI consults, ARGLDs seemed to disproportionately affect Black or Hispanic patients in 2019. The variance was less prominent during the COVID-19 pandemic in our study population, especially during the reopening phase when the relative proportion of Hispanic patients with ARGLDs was decreased by nearly two-thirds compared to the reference period. This change in patient demographics was not the result of limitations in healthcare access due to language barriers or socioeconomic status.

One of the strengths of our study is the size and composition of our study population, owing to the fact that our hospital system is the largest healthcare provider in the state with a wide catchment area. We believe findings from our study are generalizable to other urban/suburban patient populations with similar socioeconomic distributions. Another strength of our study is the use of primary clinical data, namely data exported directly from the electronic medical record system and diagnoses extracted from the original consult notes. We were thus able to eliminate confounders related to reporting bias or errors related to transcription and medical coding, which can occur if relying on a derivative data source (such as discharge summaries or administrative datasets).

Our study is, however, bound by the inherent shortcomings of any retrospective cohort study. We purposefully excluded patients who were admitted with a GI or liver disease but were not evaluated by the inpatient GI consult services in an effort to minimize confounders related to diagnostic errors made by a non-gastroenterologist. We also did not include any outpatient data due to confounders associated with the use of telemedicine during the pandemic. As such, our findings likely underestimate the true magnitude of disease burden. Because of variations in documentation, we were unable to assess the quantity of alcohol consumption or characterize specific psychosocial stressors.

In conclusion, our study confirms predictions made by public health experts as well as anecdotal experiences shared by many healthcare providers that the COVID-19 pandemic had led to a dramatic increase in the prevalence and severity of alcohol-related GI and liver diseases. Our results are corroborated by other published reports of increased alcohol sales and consumption since the start of the pandemic.[21] Despite improving infection rates in many regions, the long-term psychosocial, economic, and healthcare implications of the pandemic are currently unknown. With the easing of social distancing guidelines and the reopening of restaurants and bars, it is reasonable to anticipate a further surge in the incidence of alcohol use disorders. It is therefore imperative that primary care providers, gastroenterologists, and hepatologists proactively screen for alcohol use disorder, especially among younger patients who may not frequently interface with the healthcare system. Medical providers, community organizations, and the various stakeholders involved in intervention and support for patients with alcohol use disorder need to be ready to potentially serve more patients that prior to the pandemic. Further studies are needed to evaluate the long-term impact of COVID-19 on alcohol-related GI diseases, and to determine which interventions are most effective in treating these disorders in pandemic conditions in the future.

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Authors

Savan Kothadia, MD, Department of Internal Medicine, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI.

Waihong Chung, MD, Department of Gastroenterology, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI.

May Min, MD, Department of Gastroenterology, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI.

Firrah Saeed, MD, Department of Internal Medicine, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI.

James Scharfen, MD, Department of Internal Medicine, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI.

Fadlallah Habr, MD, Department of Gastroenterology, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI.

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Correspondence

Savan Kothadia, MD
Department of Internal Medicine
593 Eddy Street, Providence, RI 02903
704-564-6496
Fax 401-793-2953
skothadia2020@gmail.com

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Fentanyl and Fentanyl Analogs Detected Among Unintentional Opioid Involved Overdose Deaths in Rhode Island: January 2019–December 2021

HEIDI WEIDELE, MPH; RACHEL WIGHTMAN, MD, FACMT; KRISTEN ST. JOHN, MPH; LOUIS MARCHETTI, PhD; JEFFREY BRATBERG, PharmD; BENJAMIN D. HALLOWELL, PhD, MPH

INTRODUCTION

Starting in the fall of 2019, Rhode Island (RI) has experienced a significant increase in overdose deaths, with 435 lives lost to unintentional overdoses in RI in 2021.[1] Fentanyl, a highly potent synthetic opioid, continues to drive the overdose epidemic in RI and contributed to over 77% of overdose deaths in 2021. These deaths also include those attributable to fentanyl analogs, which are chemically synthetized fentanyl derivatives, which act on the opioid receptor to produce similar analgesic effects but vary in their individual potency. Some fentanyl analogs (e.g., sufentanil) are approved pharmaceuticals; however, an evolving and expanding list of fentanyl analogs without known medical use (e.g., acetylfentanyl, furanylfentanyl) have been detected in the drug supply in Rhode Island and nationally.[2] Data on pharmacokinetic and pharmacodynamic properties of fentanyl analogs in humans is limited and much of the available data is derived from animal models and invitro study limiting our knowledge on the safety of these substances.

Fentanyl and fentanyl analogs were first detected in RI in 2013. Due to notable increases in overdose deaths caused by fentanyl and fentanyl analogs they have been a concern in RI for many years.[3,4] Over time, other potent fentanyl analogs, such as carfentanil, have been detected in RI and neighboring states.[5] To better address the overdose epidemic, this work aims to better understand the role of fentanyl and fentanyl analogs among unintentional opioid-involved deaths in RI and how the presence of fentanyl analogs has changed over time.

METHODS

We used RI's State Unintentional Drug Overdose Reporting System (SUDORS) to identify opioid overdose deaths that were unintentional or undetermined in intent, and occurred in Rhode Island from January 1, 2019 to December 31, 2021. SUDORS is a standardized Centers for Disease Control and Prevention (CDC) database that collects overdose deaths from states regardless of state-specific testing protocols. Using toxicological data generated at the RI State Health Laboratories, SUDORS records the substances detected at time of death, as well as those contributing to the cause of death as determined by the medical examiner, including information on fentanyl, specific fentanyl analogs, and select metabolites.

Fentanyl analogs that were not detected during this timeframe and analogs that were detected in fewer than 5 deaths (benzylfentanyl, butyrylfentanyl, cyclopropylfentanyl, furanylfentanyl, and valerylfentanyl) were excluded to comply with Rhode Island Department of Health's (RIDOH) Small Numbers Policy.

Our final analysis assessed the detection and contribution of fentanyl and fentanyl analogs by year of death. Fentanyl analogs present in the analysis included acetylfentanyl, carfentanil, and fluorinated analogs (*p*-fluorofentanyl and *p*-flourobutyryl, which are grouped together in SUDORS despite being separate compounds). A flag was created to identify deaths which involved only fentanyl analogs (in the absence of fentanyl), and those for which no fentanyl/fentanyl analogs were involved. Results were also stratified by other substances detected at the time of death. All analyses were performed in SAS [Version 9.4].

FINDINGS

From January 1, 2019 to December 31, 2021, 965 individuals experienced a fatal opioid-involved overdose in Rhode Island. Of these, fentanyl and/or fentanyl analogs contributed to the cause of death in 86% (n=834) of deaths (**Table 1**). During this period, the proportion of unintentional opioid-involved deaths involving fentanyl or fentanyl analogs has increased from 84% to 89%. In only 2% of deaths (n=16) did fentanyl analogs contribute to the cause of death in the absence of fentanyl.

When looking at the role of fentanyl and fentanyl analogs over time, the proportion of deaths in which fentanyl was detected increased from 80% in 2019 to 88% in 2021 (**Figure 1**). The proportion of deaths in which acetylfentanyl was detected remained relatively constant over time, from 6% in 2019 to 8% in 2020 and 2021 (**Figure 2**). In contrast, the presence of carfentanil has been declining; with carfentanil detected in 5% of opioid-involved overdose deaths in 2019, 2% of deaths in 2020, and fewer than 1% of deaths in 2021. Deaths in which *p*-fluorofentanyl analogs were detected increased from 0% in 2019, to 1% in 2020, and to 13% in 2021. When looking at the presence of fentanyl

Table 1. Fentanyl and Fentanyl Analogs Detected at Time of Death, Rhode Island, 2019–2021

Substance	N (%)
Acetyl Fentanyl	
Detected	72 (7%)
Cause of Death	44 (5%)
Carfentanil	
Detected	20 (2%)
Cause of Death	20 (2%)
Fentanyl	
Detected	821 (85%)
Cause of Death	818 (85%)
P-Fluorofentanyl	
Detected	52 (5%)
Cause of Death	25 (3%)
Analogs Only (no fentanyl)	
Detected	15 (2%)
Cause of Death	16 (2%)
No Fentanyl or Analogs Present	
Detected	129 (13%)
Cause of Death	131 (14%)
Total Opioid Overdoses	**965 (100%)**

Source: State Unintentional Drug Overdose Reporting System
Note: Categories are not mutually exclusive. Multiple substances and fentanyl analogs can be detected in the same overdose. For overdoses where no fentanyl or analogs were present, other illicit or prescription opioids were detected or contributed to the cause of death.

Figure 1. Proportion of Unintentional Opioid Overdose Deaths Where Fentanyl Was Detected, Rhode Island, 2019–2021

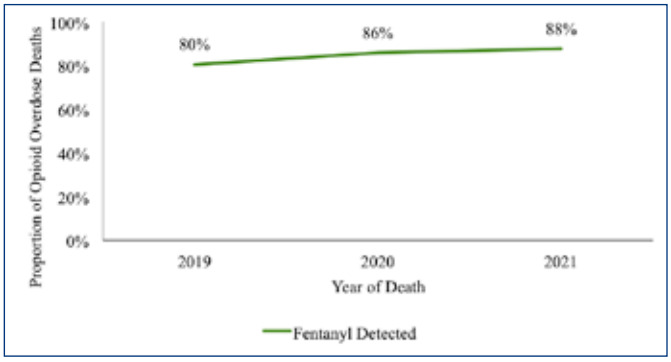
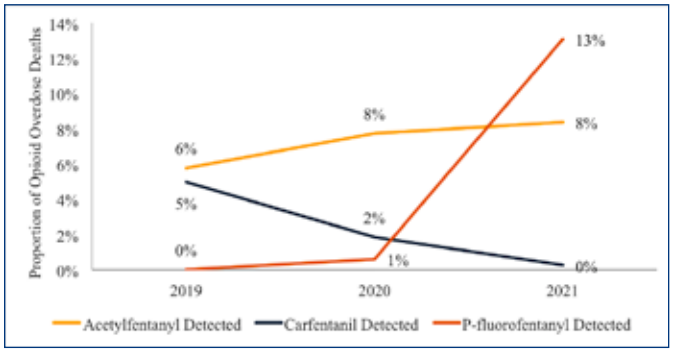


Figure 2. Proportion of Unintentional Opioid Overdose Deaths Where Fentanyl Analogs Were Detected, Rhode Island 2019–2021



analogs with other substances detected at the time of death (such as stimulants, central nervous system depressants, alcohol, and cannabis) no fentanyl analogs appeared to be solely associated with a particular co-exposure.

DISCUSSION

Our findings reaffirm the steadily growing prevalence and danger of fentanyl as it contributes to overdose deaths in Rhode Island. Fentanyl was detected and contributory to the cause of death in the majority of opioid-involved unintentional overdose deaths during the study period. Despite the growing concern of fentanyl analogs present in the drug supply, the results from this analysis indicate that most fentanyl analogs captured by SUDORS were either not detected, were found in fewer than 5 overdoses, or, if present, co-occur in the presence of fentanyl. Using all opioid overdose involved deaths occurring between 2019 and 2021, only 2% of deaths were attributed to fentanyl analogs in the absence of fentanyl. These results are promising for interventions such as fentanyl tests strips which rely on the presence of fentanyl and/or specific analogs to return a positive result.

While carfentanil was of concern locally due to having a potency ten thousand times that of morphine,[6] it is encouraging to see its sharp decline in RI since 2019 as it was detected in fewer than 5 opioid-involved overdose deaths in 2021. Acetyl fentanyl and *p*-fluorofentanyl, while increasing in prevalence, are more often detected among overdoses and in combination with fentanyl, rather than contributing to death according to medical examiner assessment. These findings align with trends observed among non-fatal overdoses in Rhode Island, as *p*-fluorofentanyl was first detected in non-fatal toxicology data starting in November 2020 and continued to appear in samples throughout 2021.[7] Similarly, acetyl fentanyl was detected in an average of 4% of non-fatal overdoses during a similar timeframe.[7]

Other studies have found that drug classes, such as stimulants, have been found to be increasingly contaminated with fentanyl over time[8]; contributing to the growing burden of polysubstance overdose deaths.[9] This should be taken into consideration when promoting harm reduction practices, as individuals may be hesitant to utilize tools such as fentanyl test strips or naloxone in situations where they intend to use substances other than opioids or in combination with opioids. This concern is further supported by local data from

testRI, which has detected fentanyl in substances that were sold as non-opioids, including crystal meth, crack cocaine, and powder cocaine.[10]

This study is subject to several limitations. First, a standard analysis for fentanyl analog confirmation among overdose deaths did not exist prior to June of 2021. Samples from suspected opioid overdoses that screened positive for fentanyl and were confirmed by tandem mass spectrometry were not required to be analyzed for fentanyl analogs. Testing for analogs was only performed for overdose deaths in which fentanyl was indicated by ELISA but undetected through confirmatory analysis. As such, the presence of fentanyl analogs in overdose deaths is likely higher than reported; however, due to the testing protocol, the proportion of deaths in which fentanyl analogs contributed to the cause of death in the absence of fentanyl is as reported. Second, new fentanyl analogs appear in the drug supply more quickly than the test panel can be updated. There are likely analogs that were missed due to a lag in updating the test panel. Third, SUDORS does not contain information on all fentanyl metabolites (including norfentanyl) so it is possible the true proportion of deaths where fentanyl was present is higher than shown.

Further studies are planned that utilize data from SUDORS to better understand the role of fentanyl and/or fentanyl analogs with polysubstance use and describe the presence of other substances detected and contributing to the cause of death. Additional work is also planned to utilize results from RI's biosurveillance system to compare toxicology data obtained from non-fatal opioid overdoses to the fatal opioid overdoses reported by SUDORS.

The findings from this work reaffirm the steadily growing prevalence and danger of fentanyl in RI, with over 89% of opioid overdose deaths in 2021 involving fentanyl and/or fentanyl analogs. These results emphasize the need to continue promoting harm reduction practices through efforts such as naloxone distribution and training, dissemination of fentanyl test strips, and continued education on the role of fentanyl in the drug supply, as well as more innovative approaches such as establishing harm reduction centers in the state.

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Authors

Heidi R. Weidele, MPH, Senior Fatal Overdose Epidemiologist, Center for Health Data and Analysis (CHDA) at RIDOH.

Rachel Wightman, MD, FACMT, Assistant Professor Emergency Medicine, Alpert Medical School of Brown University.

Kristen St. John, MPH, Substance Use Epidemiologist, CHDA, RIDOH.

Louis Marchetti, PhD, Center for Clinical Toxicology and Laboratory Support, Rhode Island State Health Laboratories.

Jeffrey Bratberg, PharmD, Department of Pharmacy Practice, University of Rhode Island College of Pharmacy.

Benjamin D. Hallowell, PhD, Substance Use Epidemiology Program Manager, CHDA, RIDOH.

Correspondence

Heidi Weidele, MPH
Senior Fatal Overdose Epidemiologist
Substance Use Epidemiology Program
Center for Health Data and Analysis
Rhode Island Department of Health
Heidi.Weidele@health.ri.gov

UTPALA BANDY, MD, MPH
INTERIM DIRECTOR, RHODE ISLAND DEPARTMENT OF HEALTH
EDITED BY SAMARA VINER-BROWN, MS

Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	APRIL 2022	12 MONTHS ENDING WITH APRIL 2022	
	Number	Number	Rates
Live Births	868	11,524	10.9*
Deaths	829	11,367	10.7*
Infant Deaths	2	40	3.5#
Neonatal Deaths	2	33	2.9#
Marriages	427	6,592	6.2*
Divorces	180	2,692	2.5*

* Rates per 1,000 estimated population
# Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	OCTOBER 2021	12 MONTHS ENDING WITH OCTOBER 2021		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	194	2,363	215.3	3,764.0
Malignant Neoplasms	194	2,169	197.7	4,280.0
Cerebrovascular Disease	55	434	41.7	497.5
Injuries (Accident/Suicide/Homicide)	105	1,032	94.0	14,579.5
COPD	40	369	33.6	395.0

(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.

Thanks to RIMJ's Guest Editors of 2022

This issue marks the completion of a decade of the e-publication format of the *Rhode Island Medical Journal* (RIMJ), which transitioned to an online-only journal in 2013. Although the platform of the Journal has changed to a digital one, its mission remains the same as it has for the past 105 years – to be the medical journal of record for the state.

Going digital and a LinkOut icon to free articles indexed on PubMed.gov has enhanced its scope exponentially; this year the Journal has reached approximately 50,000 unique viewers worldwide to date.

As RIMJ is about to enter its 106th year, we thank the guest editors and contributors of this year and over the decades. Without them and the support of its publisher, the Rhode Island Medical Society (RIMS), and its Board, as well as RIMJ's Editorial Advisory Board, the success of the Journal for more than a century would not be possible. ❖


APRIL 2022
PUBLIC HEALTH ETHICS
JOSEPH H. WU, PhD, MD'23; ELI Y. ADASHI, MD, MS
GUEST EDITORS

Introduction: Public Health Ethics
JOSEPH H. WU, PhD, MD'23
ELI Y. ADASHI, MD, MS

Non-Maleficence, Social Benefit and the Vaccination of Children
STEPHEN JOHN, PhD

Ethics of Advocacy
LYNETTE REID, PhD

Melanoma Screening: The Ethics of Over- and Underdiagnosis
JOSEPH H. WU, PhD, MD'23
NICOLE A. NEGBENEBOR, MD

Wandering Virtues, Moral Confusion
MICHAEL FELDER, DO, MA
EZRA FELDER, BA, DO'26

Towards an Improved Substance Use Disorder Treatment Landscape in Rhode Island – Barriers, Current Progress, and Next Steps
HANNAN MOSES BRAUN, MD
JULIETTE A. HOLTZMAN, LICSW, LCDP
CAROLINE WUNSCH, MD
SETH A. CLARK, MD, MPH

On the Ethics of Mandatory Reporting of Positive Drug Tests in Newborns and Pregnant Parents at the Time of Delivery
JONATHAN SPIEGEL, ScB, AB, MD'23
GREGORY COHAN, AB, MD'23
E. CHRISTINE BROUSSEAU, MD
ELIZABETH TOBIN-TYLER, JD, MA


MAY 2022
SUICIDAL BEHAVIOR IN CHILDREN AND ADOLESCENTS
ANNE S. WALTERS, PhD; JENNIFER C. WOLFF, PhD
GUEST EDITORS

Introduction
ANNE S. WALTERS, PhD
JENNIFER C. WOLFF, PhD

A Comparison of Acute Mental Health Presentations to Emergency Services Before and During the COVID-19 Pandemic
MARY KATHRYN CANCILLIERE, PhD
KATHLEEN DONISE, MD

Single- vs. Multi-Item Assessment of Suicidal Ideation Among Adolescents
ILANA GRATCH, BA
KATHERINE M. TEZANOS, MS
SARA N. FERNADES, MA
KERRI-ANNE BELL, MA
OLIVIA H. POLLAK, BS
CHRISTINE B. CHA, PhD

Assessing the Quality of Patient Responses to a Psychosocial Intervention Implemented on an Adolescent Psychiatric Inpatient Unit: Devising the Safety Plan Quality Metric
PAULINE H.L. BAGATELAS, MD'22, ScM'22
JEFFREY I. HUNT, MD
JENNIFER C. WOLFF, PhD

Suicide Risk and Psychotic Experiences: Considerations for Safety Planning with Adolescents
ELIZABETH C. THOMPSON, PhD
MARGARET NAIL, BS
SHIRLEY YEN, PhD

Raising Children in Different Cultures: Working with Latinx Youth with Suicidal Behaviors and Their Families
GISELA JIMENEZ-COLON, PhD
YOVANSKA DUARTE-VELEZ, PhD

Recognizing Suicidal Risk in Very Young Children
ELIZABETH WAGNER, MD, MPH
ANJALI GOTTIPATY, BA
JEFFREY I. HUNT, MD
JOHN R. BOEKAMP, PhD

JUNE 2022
REFLECTIONS ON MEN'S HEALTH
MARK R. PAULOS, MD
GUEST EDITOR

The Evolution of Men's Health
MARK R. PAULOS, MD

Men's Health Centers: An Emerging Paradigm of Sexual Function and Cardiometabolic Risk Reduction
MARTIN M. MINER, MD
MARK PAULOS, MD
VINCENT HARISARAN, MD

ED & Cardiometabolic Risk Stratification: Can This Be Done on an Asynchronous Platform?
MYLES SPAR, MD, MPH
MARTIN M. MINER, MD

Perspective: The Paradox of Men's Health
YUL D. EJNES, MD

HeadsUpGuys: An E-Mental Health Resource for Men with Depression
JOHN S. OGRODNICZUK, PhD
JOSHUA BEHARRY, BSc
JOHN L. OLIFFE, PhD

Preconception Considerations for Male Fertility
DAVID P. GUO, MD

SEPTEMBER 2022
THE EVALUATION & REHABILITATION OF LONG COVID
JON A. MUKAND, MD, PHD
GUEST EDITOR

Introduction: The Evaluation & Rehabilitation Of Long Covid
JON A. MUKAND, MD, PhD

A Review of Respiratory Post-Acute Sequelae of COVID-19 (PASC) and the Potential Benefits of Pulmonary Rehabilitation
MICHAEL SIMON, MD
JAMES E. SIMMONS, MD

Long-term Cardiovascular Manifestations and Complications of COVID-19: Spectrum and Approach to Diagnosis and Management
VISHAL KHETPAL, MD
JULIA BERKOWITZ, MD
SHILPA VIJAYAKUMAR, MD
GAURAV CHOUDHARY, MBBS
JON A. MUKAND, MD, PhD
JAMES L. RUDOLPH, MD, SM
WEN-CHIH WU, MD, MPH
SEBHAT ERQOU, MD, PhD

Neurological Sequelae of COVID-19 in Rehabilitation Settings
KATHERINE A. STILES, MD
EMILY WEISBACH, MD
JONATHAN F. CAHILL, MD

Cognitive Complications of COVID-19 Infection
SCOTT WARREN, MD, PhD
JONATHAN DRAKE, MD, MS
CHUANG-KUO WU, MD, PhD

Long-term Orthopedic Manifestations of COVID-19: Heterotopic Ossification and Digital Necrosis
JONATHAN LIU, MD
LAUREN LUTHER, MD
SHASHANK DWIVEDI, MD
ANDREW R. EVAN, MD

OCTOBER 2022
OSTEOPOROSIS, METABOLIC BONE DISEASES, AND FRAGILITY FRACTURES
JAKE LITTMAN, ScM, MPH; ROY K. AARON, MD
GUEST EDITORS

Preface: The Fracture Liaison Service
JAKE LITTMAN, ScM, MPH
ROY K. AARON, MD

The Roles of a Fracture Liaison Service
JAKE LITTMAN, ScM, MPH
ELKA ARREDONDO, DPT
MARISA COSTA
ROY K. AARON, MD

Osteoporosis and Fragility Fractures
EDWARD J. TESTA, MD
TUCKER C. CALLANAN, MD
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ROY K. AARON, MD

Osteomalacia and Renal Osteodystrophy
JACOB M. MODEST, MD
HIMESH SHETH, MD
REGINALD GOHH, MD
ROY K. AARON, MD

Monoclonal Gammopathies in a Fracture Liaison Service
BRITTANY MCCALL, MD
ZAINAB IBRAHIM, MD
PETER BARTH, MD
ROY K. AARON, MD

Hyperparathyroidism in a Fracture Population
GILLIAN LEE, MD, MPH
TRAVIS COTTON, MD
JOSEPH TUCCI, MD
ROY K. AARON, MD

Vertebral Compression Fractures
CHRISTOPHER L. McDONALD, MD
DANIEL ALSOOF, MBBS
ALAN H. DANIELS, MD



NOVEMBER 2022
PART 1: UPDATES IN INFLAMMATORY BOWEL DISEASES

ABBAS H. RUPAWALA, MD; JASON M. SHAPIRO, MD; SAMIR A. SHAH, MD
GUEST EDITORS

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

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

Extraintestinal Manifestations of Inflammatory Bowel Disease
SEAN FINE, MD, MS

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

Treat-to-Target: The Era of Targeted Immunosuppressive Agents in IBD Management
DANIEL MARINO, MD, MBA
SIDDHARTH SINGH, MD, MS
JASON HOU, MD, MS
COREY SIEGEL, MD
GIL MELMED, MD
SAMIR A. SHAH, MD



DECEMBER 2022
PART 2: UPDATES IN INFLAMMATORY BOWEL DISEASES

JASON M. SHAPIRO, MD; ABBAS H. RUPAWALA, MD; SAMIR A. SHAH, MD
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Inflammatory Bowel Disease in Children and Adolescents
SHOVA SUBEDI, MD
ALLISON L. BEHRLE YARDLEY, MD
JASON M. SHAPIRO, MD

Approach to Inflammatory Bowel Disease in Pregnancy
DANA LEY, MD
SUMONA SAHA, MD, MS

Management of the Hospitalized Patient with Acute Colitis
ABBAS H. RUPAWALA, MD
ERIC MAO, MD
CHARLES BALDI, MD
ADAM KLIPFEL, MD

Surgical Management of Inflammatory Bowel Disease
VINCENT P. ANTO, MD
AARON J. DAWES, MD, PhD
MATTHEW VREES, MD
ANDREW R. WATSON, MD
AMY L. LIGHTNER, MD

Nutritional Management of Inflammatory Bowel Disease
RAHIYA REHMAN, MD
BETH PINKOS, MS, RDN
JASON M. SHAPIRO, MD
CAROLINA CEREZO, MD

Lessons Learned from the Ocean State Crohn's and Colitis Area Registry
JASON M. SHAPIRO, MD
NEAL S. LELEIKO, MD, PhD
BRUCE E. SANDS, MD
SAMIR A. SHAH, MD

Effects of COVID-19 on Patients with Inflammatory Bowel Disease
LAWRENCE KOGAN, MD
RYAN C. UNGARO, MD
FREDDY CALDERA, MD
SAMIR A. SHAH, MD

Rhode Island and the Changing Paradigm of Health Care Delivery

WILLIAM BINDER, MD

One year ago, prior to the failure of the proposed merger of Lifespan and Care New England, I wrote about the declining state of health care in Rhode Island.[1] Despite Rhode Island's numerous challenges, local physicians, nurses, advanced practice providers, and other health care workers have toiled relentlessly, attempting to provide the standard of care to our catchment area. Hope springs eternal and there was a sliver of optimism at that time – the COVID-19 vaccine had demonstrated proven effectiveness in spite of a surge in cases, a potential merger offered new resources to cash-strapped health systems, and for a while, the economy surged.

> Markers of ED operational efficiency are the canary in the coal mine.

Unfortunately, the fault lines unearthed by the pandemic have not healed and, in fact, have widened. The lessons of the pandemic have gone unheeded. The innovation, support, and collaboration between public and private entities noted in the early days of COVID-19 have dissipated. Emergency physicians in Rhode Island's largest health care system have seen conditions deteriorate even further than we thought possible. It is difficult to look a patient in the eye while he or she is writhing in agony from a kidney stone, or vomiting due to a bowel obstruction, and tell them you can help alleviate their pain, knowing full well that inadequate staffing means no one is available to implement an order in a timely manner.

There are numerous causes for Rhode Island's health care dysfunction. Locally, a poor business climate, an often tumultuous relationship between health systems and unions, leadership vacuums, and myopic vision have resulted in a challenging environment. The two largest health systems are teetering on the brink of insolvency. However, larger forces are also at work throughout the United States (US). The current structure of health care financing, a lack of inpatient capacity nationally (emergency department (ED) visits have risen over the past 2 decades, while the number of EDs and inpatient beds has decreased), staffing shortages, issues surrounding behavioral health care and opioid and substance use disorders, as well as diminished outpatient health care availability, have strained our system.[2]

THROUGH THE ED LENS

Length of stay, inpatient boarding

The health of a hospital can be revealed through the lens of its ED. Markers of ED operational efficiency are the canary in the coal mine.[2] One important metric, length of stay (LOS), has risen dramatically in all of Rhode Island's EDs due to inpatient boarding. While increased boarding and LOS have risen nationally, some of the state's facilities are double the national average. Boarding, a result of inadequate nurse staffing on inpatient floors and an inability to discharge patients to skilled nursing facilities (which are beset with their own staffing problems) has downstream implications. Medical errors are likely to increase, patient privacy is compromised, and there is increased mortality among patients who wait greater than 4 hours for a bed.[3] In Rhode Island hospitals, where the majority of patients are admitted through the ED, boarding leads to ED crowding, a sentinel marker of hospital dysfunction.[2] Panicked parents of infants requiring suctioning due to RSV bronchiolitis arrive to the ED after referral by their pediatrician, only to be told it is an 8–9 hour wait. Staff are demoralized as well. There are ED shifts in which we have 4 open beds for 60 unsuspecting patients, leaving these poor souls to linger hours and hours in a crowded waiting room. Frequently, patients wait, but some – too many – do not.

Left without being seen

Left without being seen (LWBS), perhaps the most sensitive metric regarding ED function and throughput, has surged nationally and locally. Median LWBS in the US has doubled from 1.1% to 2.1% between 2017–2021, numbers which would have been welcome for most Rhode Island hospitals *preceding* the pandemic.[4] The worst performers in a national study averaged 10% LWBS toward the end of 2021, and this was prior to the recent explosion in non-COVID-19 respiratory viruses.[4] Unfortunately, pre- and post-pandemic, Rhode Island's hospitals are at the back of the pack, with some facilities now running in the double digits.

Impact

The impact of long waits, ED boarding, and inadequate staffing has subtly changed our approach to health care. Colleagues in every field, from emergency medicine to psychiatry to hospitalists to orthopedics, are making decisions based on resource scarcity rather than on the standard of care. We send home patients whom we would normally observe or admit, and ask them to see their primary care physician, whose first available appointment may be in 3 months. Any small perturbation threatens to drive the system further into crisis. The recent epidemic of RSV infections in pediatric and vulnerable adult patients is a case in point, and has led to extended and dangerous delays in emergency care.

SOLUTIONS TO CONSIDER: SCOPE OF WORK

EMTS

Under current conditions, we are not meeting the needs of our patients, nor of our health care workers. Some immediate solutions to this crisis are available, but require insight and courage. The paradigm of health care delivery has changed. Rhode Island Department of Health (RIDOH) regulations prevent EMTs or paramedics from placing intravenous lines in an ED, yet somehow it is reasonable for the same provider to place an IV while in an ambulance bouncing around. In contrast, paramedics routinely insert IVs in Massachusetts hospitals. Recently an emergency order was submitted by RIDOH to allow EMTs to place IV lines in the ED. This needs to be a permanent change, and suggests that all allied health roles should be reevaluated given personnel shortages.

Nursing

A more complicated problem is nursing. Over the last several decades, and in response to the Institute of Medicine's 2010 report on nursing, the nursing profession has been encouraged to accept greater responsibilities within the health care system.[5] The pandemic has upended the equation and created a supply chain deficit throughout the US. The impact on Rhode Island has been profound. Every hospital in the state is insufficiently staffed and our patients suffer. Entire units have closed in EDs and on inpatient floors, dramatically reducing capacity at a time when we cannot afford the loss of a single bed. While nursing is an important and crucial part of the health care system, in an era of scarcity, nursing roles must be reevaluated and responsibilities have to be pared down to essential tasks. Nursing leadership and the unions need to consider unconventional, yet forward thinking solutions for change.

Expanding resources at state level

Additional changes could be considered at the state level. Behavioral health resources and beds can be expanded, alleviating an enormous stress on our system, but this will take time and money. However, boarding behavioral health patients comes at its own cost. Many of our patients with behavioral health issues and those with substance abuse disorders frequently remain in the ED for 24 to 48 hours, or longer, despite stabilization and a thorough assessment, because they have nowhere to go. This prevents 5–6 ED patients per day per boarder from being seen. Coordination (and funding) between the state and our hospitals could alleviate the impact of mental health boarding.

CONCLUSION

The techs, advanced practice providers, nurses, and physicians who come to work daily routinely experience the frustration of a system stymied by roadblocks. We are in uncharted territory and we have choices. We can hope for improvement, or we can redesign our approach to patient care and increase our capacity, and allow health care workers to perform at the top of their abilities. It is heartbreaking to watch conditions deteriorate when solutions to our crisis are within reach. In order to deliver high quality health care in Rhode Island, it is essential that state government, RIDOH, the state's health systems, unions, nurses, and physicians and providers recognize that the ground has shifted. In adversity there can be opportunity. It is time for immediate action. ❖

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Author

William Binder, MD, Associate Professor of Emergency Medicine, Warren Alpert Medical School of Brown University; Attending Physician, Rhode Island Hospital, The Miriam Hospital; Editor-in-Chief, *Rhode Island Medical Journal.*

Correspondence

william_binder@brown.edu

It's Never the Right Time to Say Goodbye…Until It Is: Transitioning from Pediatric to Adult Primary Care

ASHLEY T. NGUYEN, MD; CAROL LEWIS, MD; MEGHAN GEARY, MD

The transition from childhood to adulthood has the potential to be full of excitement and possibility. However, it may also be full of the unknown, change, and stress. Young adults will need to transition their medical care from their pediatrician to a new adult primary care provider.[1] Young adults are defined as 18–21 years of age by the American Academy of Pediatrics (AAP)'s Health Children organization.2 The transition from pediatric to adult health care is often associated with poor outcomes in young adults and may be associated with various challenges.3 When compared to other groups, young adults have lower rates of health care system utilization, higher rates of emergency room visits, and lower rates of health insurance coverage.3 Young adults may experience health disparities due to unique challenges that marginalized youth encounter in our health care system, including discrimination and lack of access to health care, which may ultimately lead to worse physical and mental health outcomes.4 Improving the health care transition process may improve the long-term health and well-being of young adults, which will benefit not only individual young adults but also the healthcare system as a whole.

Health Care Transition (HCT) Program

Although there are national resources for the transition of young adult patients, the Health Care Transition (HCT) Program at Hasbro Children's Hospital (HCH) and the Rhode Island Hospital (RIH) is unique to our institutions. The HCT aims to address potential challenges in the transition of patients from pediatric to adult heath care. The program hopes to eliminate discontinuities in care, prepare adolescents for an adult model of care, identify available adult providers, transfer pediatric patients to adult primary care, and facilitate communication between pediatric and adult providers.3 Both HCH Pediatric Primary Care and the Center for Primary Care of RIH identified a total of 2507 patients that will benefit from high-quality primary care that is focused on young adult health care. There were 1926 patients identified who were between 12 to 18 years old, and who will need transfer to adult primary care in the next 6 years or less. The importance of identifying a structure to support and facilitate the transition of youths to adult health care was demonstrated.

The six core elements in the process of health care transition were identified in the Clinical Report on HCT by the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Physicians.5 Using these fundamental elements, our HCT Program aimed to create a structure to enhance our current efforts with transition care. The pilot program aimed to transfer 5 pediatric patients to adult primary care. These 5 pediatric patients represented a diverse patient population with 1 patient having complex medical care needs, 1 patient having mental health needs, and 3 patients without significant health issues (**Figure 1**). The pilot program was executed over the course of a year. After the pilot program experienced success with transitioning and transferring 4 out of 5 pediatric patients from HCH Pediatric Primary Care to the Center for Primary Care, we took the opportunity to expand the HCT Program (**Figure 2).** We recruited a second adult primary care office, the Fain Health Center associated with The Miriam Hospital. Significant commonalities between these three sites include having similar resident-faculty practice models, sharing the same electronic medical record, and serving predominantly Medicaid-insured patients.

Figure 1. Description of Patients in the Pilot Program

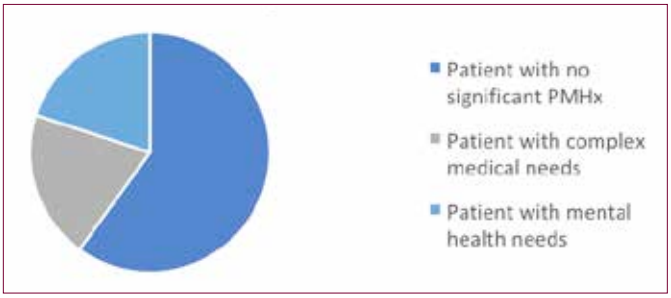
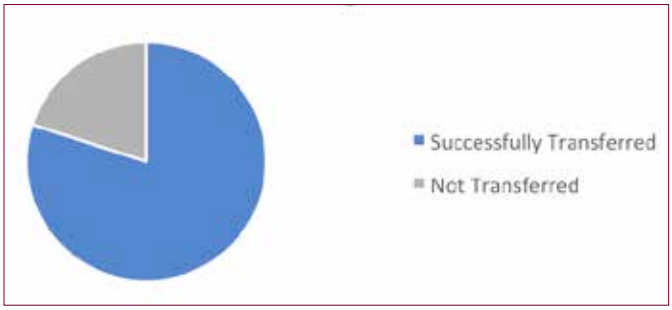


Figure 2. Patients Transferred to Adult Primary Care in the Pilot Program



The pilot program provided many informative lessons. We learned that adult providers appreciated adding new young adult patients onto their patient panels, receiving a holistic picture of the new young adult patient, and knowing that they could easily contact the prior pediatrician if they had any questions about the patient. Additionally, we learned that pediatric providers had an easier time letting go of their pediatric patients who they may have formed long-term and meaningful therapeutic relationships with. Pediatric providers found this transition and transfer easier since they knew who their patient was going to be cared for by next. In addition to benefits to both adult and pediatric providers, we learned that the HCT Program strengthened interdepartmental relationships between adult and pediatric providers. Increased interdepartmental collaboration has the potential to not only provide an environment to share ideas but also to advance the health care of young adults. A challenge identified was ensuring that the young adult patient keeps their first scheduled adult primary care practice appointment. Contacting patients was challenging, and text communication may be more effective in the future. Of note, 1 patient no-showed their first adult primary care appointment, emphasizing that additional work needed to be done to ensure completion of the first visit.

Engaging medical residents

With a framework for transferring patients in place and with the pilot program having success, our focus expanded to further engaging and involving medical residents. We executed two educational conferences about the importance of health care transition and about the HCT Program. One of these conferences was for both internal medicine and pediatrics residents to attend, which also provided an opportunity for interdepartmental connections. Additionally, a formal opportunity was held to allow residents from the Departments of Internal Medicine, Pediatrics, and Internal Medicine-Pediatrics to network professionally and to build connections in order to better transfer pediatric patients to adult primary care. Special interest in subgroups of young adult health care exists amongst resident physicians. These subgroups include women's health, LGBTQ+ health, and patients aging out of foster care. We have also acknowledged the strengths of pediatric providers in regards to obtaining thorough social histories using screening tools such as the HEADSS assessment, and the importance of teaching adult providers these skills to better evaluate and care for issues that may affect young adults such as eating disorders or bullying.

The transition from the pediatric to adult model of care is one of the many aspects of change that young adults may experience. There is significant potential to improve the long-term health of individual young adults but also ameliorate the long-term cost on the healthcare system. The HCT Program at HCH and RIH successfully implemented a structure to transition and transfer pediatric patients to adult primary care, and has expanded to transfer 35 additional pediatric patients over the next academic year. Our hope is that we can further expand and establish the HCT Program to facilitate the high-quality transition and transfer of many pediatric patients moving forward.

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Authors

Ashley T. Nguyen, MD, Department of Internal Medicine-Pediatrics at Brown University, Rhode Island Hospital and Hasbro Children's Hospital, Providence, RI.

Carol Lewis, MD, Department of Pediatrics at Brown University, Hasbro Children's Hospital, Providence, RI.

Megan Geary, MD, Department of Medicine at Brown University, Rhode Island Hospital, Providence, RI.

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Correspondence

Ashley T. Nguyen, MD
Internal Medicine-Pediatrics at Brown University
245 Chapman Street
Providence, RI 02905
anguyen@lifespan.org

We are read everywhere

In 2022, more than **45,000** unique viewers from **120** countries have read articles in the *Rhode Island Medical Journal* or researched topics in its archives.

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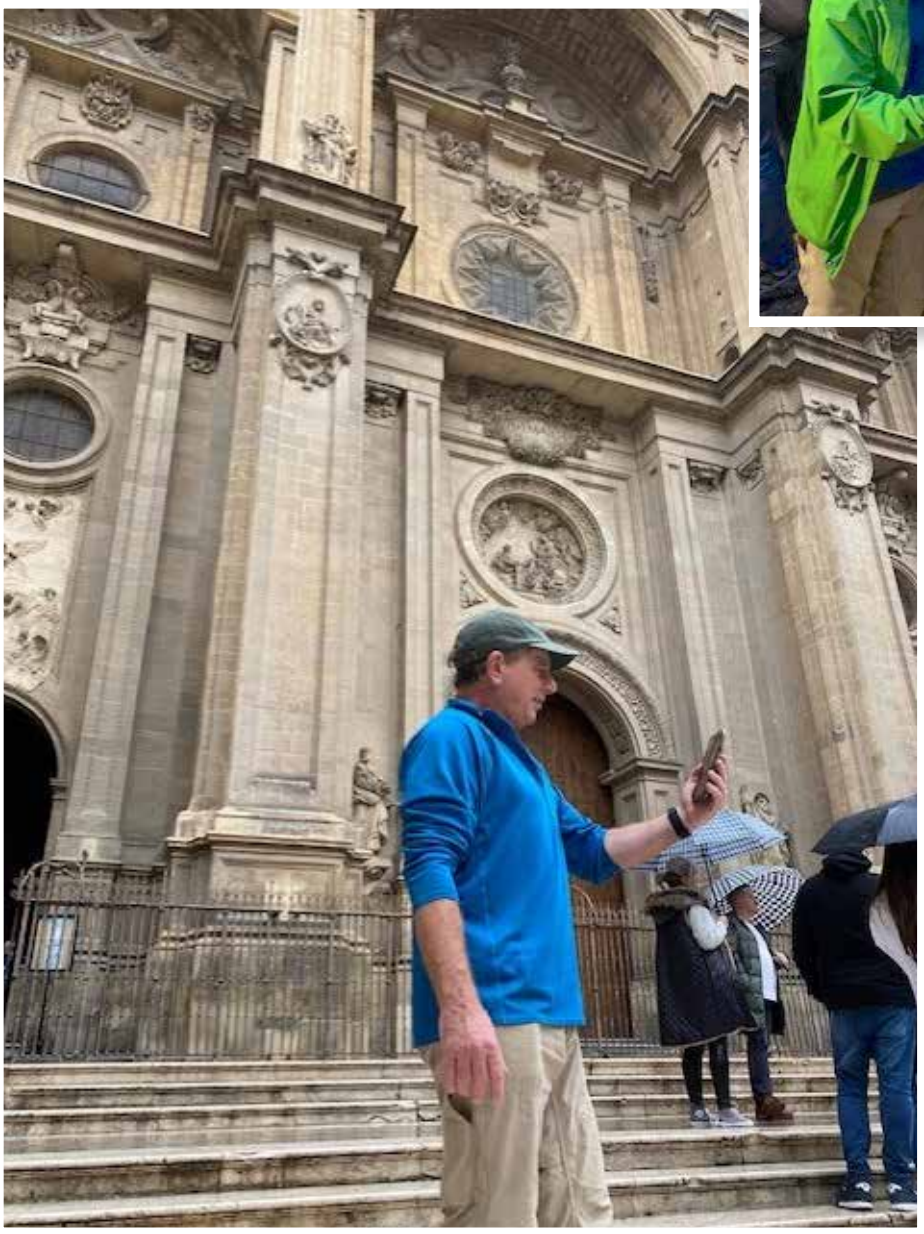

SPAIN

Córdoba

RIMJ Editor-in-chief **William Binder, MD**, checks the latest issue of the Journal in front of the bronze seated statue of Mosén Ben Maimón, Maimónides (1138–1204) in the Plaza de Tiberiades in Córdoba. Created by sculptor Amadeo Olmos Ruiz, it was unveiled in 1964. Philosopher, Hebrew theologian and physician, Maimonides was born to a Sephardic Jewish family and lived in Córdoba in the 12th century. After the city was conquered by the Berber dynasty in 1148, the family of Maimonides moved throughout southern Spain for 10 years, and then to Morocco, before settling in Egypt, in the old capital of Fustat, now Cairo. Here he studied medicine and ultimately became physician to the Sultan Saladin in 1180. He died in Egypt in 1204 and is buried in Tiberias, Israel.

Granada

The Cathedral de Granada was built upon the site of the Great Mosque. Construction began in 1523 with the foundation and finished in 1704. It took, in total, 181 years to be built. Although the initial designs were of Gothic style, the Cathedral was mainly constructed during the Spanish Renaissance period. The Cathedral has impressive facades and a stunning interior with a grand altar and several chapels. It is the 4th largest Cathedral in the world.

Wherever you may be, or wherever your travels may take you, check the Journal on your mobile device, and send us a photo: **mkorr@rimed.org**.

Working for You: RIMS advocacy activities

November 1, Tuesday

RIMS Physician Health Committee (PHC): **Herbert Rakatansky, MD**, Chair

Alpert Medical School Student Health Council meeting: **Kathleen Boyd, MSW**, Advisor

November 7, Monday

RIMS-Warren Alpert Medical School event with RODEO members: **Fredric Christian, MD**; **Nicholas Califano, MD**; **Virginia Schmidt Parker, MD**; **James Crowley, MD**

RIMS Board of Directors meeting: **Thomas A. Bledsoe, MD**, President

November 8, Tuesday

Rhode Island Foundation Long Term Health Planning Policy Sub-committee: Stacy Paterno, staff

Blue Cross & Blue Shield of Rhode Island (BCBSRI) update: **Thomas A. Bledsoe, MD**, President; **Elizabeth Lange, MD**, Immediate Past President

November 9, Wednesday

Rhode Island Department of Health (RIDOH) Board of Medical Licensure and Discipline (BMLD): Robert Dulski, staff

Governor's Overdose Intervention and Prevention Task Force: **Sarah Fessler, MD**, Past President

November 11–15, Friday–Tuesday

AMA House of Delegates Interim meeting: Delegates **Peter Hollmann, MD,** and **Alyn Adrain, MD**; Alternate Delegates **Sara Fessler, MD**, and **Thomas A. Bledsoe, MD**; Stacy Paterno, staff

November 15, Tuesday

National Government Services (NGS) Key Stakeholder meeting

Rhode Island Department of Health (RIDOH) Health Service Council meeting: Robert Dulski, staff

OHIC Health Insurance Advisory Committee (HIAC): **Catherine A. Cummings, MD**, Past President

Rhode Island Public Health Association annual meeting

November 16, Wednesday

RIDOH Primary Care Physicians Advisory Committee (PCPAC) meeting: **Elizabeth Lange, MD**, Immediate Past President

OHIC Administrative Simplification Task Force meeting: **Elizabeth Lange, MD**, Immediate Past President

Health Professions Loan Repayment Program Board meeting: Stacy Paterno, staff

November 17, Thursday

Rhode Island Foundation Long Term Health Planning Committee meeting: Stacy Paterno, staff

Executive Office of Health and Human Services (EOHHS) Health Information Technology (HIT) Steering Committee meeting: Stacy Paterno, staff

RIMS Climate Change and Health Committee

Johnson & Wales Center for Physician Assistant Studies: Identifying and Responding to Health Concerns for Yourself and/or Colleagues: **Raymond Cord, PA-C**, Physician Health Committee; **Kathleen Boyd, MSW,** Physician Health Program Director

Federation of State Physician Health Programs-Peer Enhancement & Effectiveness Review (PEER™) Committee (PEERC): **Kathleen Boyd, MSW,** Director, RIMS Physician Health Program, Vice-Chairperson, PEERC

November 18, Friday

Healthcare Workforce Planning Loan Repayment Discussion: Stacy Paterno, staff

November 21, Monday

Public Laws Committee Meeting: **Michael Migliori, MD**, Chair

November 22, Tuesday

Finance Committee Meeting: **Matthew Smith, MD**, Chair

Hospital Capacity Workgroup meeting: **Catherine A. Cummings, MD**, Past President; **Elizabeth Lange, MD**, Immediate Past President; **Thomas A. Bledsoe, MD**, President; **Heather Smith, MD**, President Elect; **Bradley Collins, MD**, Past President; **Dina Himelfarb, MD**, President, RI ACEP

RIMS NOTES: *News You Can Use*

Our biweekly e-newsletter is published on alternate Fridays exclusively for RIMS members. Contact Dulce Cosme if you've missed an issue, dcosme@rimed.org.

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RI hospitals, state leaders address ED crowding, wait times

PROVIDENCE – With several respiratory viruses currently circulating in Rhode Island and with the holidays coming, State health officials and hospital leaders urged the public to only go to emergency departments for issues that require emergency care. Hospital emergency departments in Rhode Island are experiencing significant crowding and prolonged waiting times.

At a recent press event, leaders reminded Rhode Islanders that many health issues can be treated quickly and effectively by a primary care provider, in an urgent care facility, or at a health center. This includes less severe cases of the flu, back pain, minor cuts, sore throats, low-grade fevers, and most cases of norovirus (the "stomach flu"). Although many outpatient settings are also currently seeing a very significant number of patients, seeking care for less serious health issues in non-hospital settings will help ensure that emergency care is available to people who truly need it.

State leaders also announced at the press event that a new, temporary health regulation will allow emergency medical services (EMS) personnel to work under the supervision of an on-site healthcare provider in a hospital or other licensed healthcare facility in Rhode Island. This regulation is in response to the staffing shortage in emergency departments, which is contributing to the overcrowding challenges at facilities. Additional measures being taken at the State level to respond to the emergency department overcrowding issue are outlined below.

"Similar to last fall and winter, we are seeing longer waits at local emergency rooms. While COVID-19 and influenza are circulating again, there are also additional challenges at hospitals throughout the country this year due to RSV, behavioral health needs, and healthcare worker shortages," said **ANA NOVAIS**, Acting Secretary of the Executive Office of Health & Human Services. "There are several steps the state is taking, in partnership with our local hospitals and providers, to ease the strain on our healthcare system but these issues are complex and require all of us to seek care in the most appropriate setting."

Rhode Island and states throughout the region are currently seeing high rates of RSV, a common virus that can be serious for some higher risk children and adults. Cases of RSV usually peak in Rhode Island in early January. Flu is starting to circulate in Rhode Island as well, and hospitals are still treating patients with COVID-19. The ongoing behavioral health crisis and the national healthcare workers shortage are creating additional challenges for the hospitals in Rhode Island, in addition to the circulation of these respiratory viruses.

At the press event, State leaders highlighted health.ri.gov/rightplace. This page has links to lists of primary care providers, urgent care centers, and health centers in Rhode Island, and guidance on when and when not to go to the emergency department. RIDOH will continue directing Rhode Islanders to this page and other resources through a statewide communications campaign, to be launched in the coming weeks.

"These past months we have experienced a steady increase in young patients needing hospitalization due largely to the early peak of the respiratory viral season. This, combined with a national staffing shortage during an ongoing severe children's behavioral health crisis, has created an unprecedented 'perfect storm' for children's hospitals nationwide. We are doing our best to creatively use our resources and expand where we can to serve the region's most vulnerable children and support our community providers where most pediatric health care is delivered," said **FRANK OVERLY, MD**, medical director, Hasbro Children's Hospital emergency department.

"Emergency Department overcrowding is a serious threat to patients and staff and has intensified through the pandemic," said **LAURA FORMAN, MD**, Chief of Emergency Medicine, Kent Hospital. "Hospital staff across the state are working to ensure that all patients have access to timely care during this crisis."

Measures being taken at the State level

An interagency team across the Executive Office of Health and Human Services (EOHHS) is working toward the development and implementation of strategies to address the challenges hospitals are facing. They include:

- Promulgating an emergency regulation allowing emergency medical services (EMS) professionals to work in hospitals and other healthcare facilities.
- Launching a broad public education campaign on seeking the right care in the right setting. Messaging is happening through social media, traditional media, schools, and other channels.
- Messaging to the primary care provider community about measures that can be taken in that setting to lessen emergency department overcrowding. Examples include making more same-day sick appointments available for patients and offering expanded and/or non-traditional office hours; and seeing patients who have non-urgent symptoms in the office or by telemedicine, instead of referring them to the emergency department.
- Expediting the licensure process to ensure that all new healthcare workers are able to join the workforce in Rhode Island as quickly as possible.
- DCYF is focusing on expediting discharges from Hasbro and Bradley Hospital, especially for children who can go home if supportive services can be made available.
- Daily, weekday meetings with BHDDH and all hospitals, BH Link and three Community Mental Health Centers with stabilization units to identify openings to place clients.
- Building the infrastructure for Certified Community Behavioral Health Clinics, which we expect to come online in FY24.
- RIDOH's PediPRN Program is available to pediatric providers to help diagnose, assess, and manage mild to moderate behavioral health issues in children
- Sharing a Family Behavioral Health Crisis Plan that is available multiple languages, to help all families plan for behavioral health emergencies.
- Launching Mobile Response Stabilization Services, which is a mobile crisis service that can help prevent youth from having to go to or stay at the Emergency Department. ❖

CharterCARE to return to nonprofit status; Centurion Foundation signs definitive agreement

PROVIDENCE – The Centurion Foundation (Centurion) and Prospect Medical Holdings, Inc. (Prospect) announced on Nov. 22nd they have signed an Asset Purchase Agreement (APA) for Centurion to acquire the CharterCARE Health Partners (CCHP) system from Prospect. Centurion also announced that QHR Health will assist in the transition process and will provide ongoing consulting support to CharterCARE senior management and board of directors.

The agreement also includes CharterCARE's related businesses, real estate assets, physician clinic operations and outpatient services, and it is subject to customary regulatory approvals, including reviews by the Rhode Island Department of Health and the Rhode Island Attorney General.

Under the APA, Centurion will purchase the assets and operations associated with the following hospitals and ancillary services that comprise CharterCARE:

- Roger Williams Medical Center in Providence, RI
- Our Lady of Fatima Hospital in North Providence, RI
- Blackstone Valley Surgicare in Johnston, RI
- CharterCARE Medical Associates in Providence, RI
- CharterCARE Home Health Services in Providence, RI
- Roger Williams Cancer Center in Providence, RI
- Southern New England Rehabilitation Center in North Providence, RI
- St. Joseph Health & Dental Center in Providence, RI

Prospect will continue to own and operate the value-based care business in Rhode Island consisting of Prospect Provider Group, an independent physician association (IPA), and Prospect Health Services of Rhode Island, which serves 72,000 members through its nearly 500 physicians and other providers in the IPA. Prospect will also continue to work closely with CharterCARE and its hospitals and ancillary entities.

Centurion is an Atlanta, GA-based nonprofit 501(c)(3) corporation organized to finance, own, and operate healthcare facilities. Its charitable mission is to increase access to and lower the cost of community-based healthcare. Centurion focuses on reinvesting operating profits into its facilities, people, and communities it serves.

Centurion will establish CharterCARE Health of Rhode Island, Inc., as a 501(c)(3) organization to acquire CCHP from Prospect. Upon closing, CCHP and its more than 2,500 employees will become a nonprofit health system seeking to increase access and lower the cost of healthcare services for the local community. Centurion of Rhode Island will maintain local leadership and will have a Board of Directors that includes local community leaders in the healthcare field.

QHR Health (QHR), based in Brentwood, TN, partners with nonprofit community hospitals and health systems to help them deliver quality healthcare and achieve results that keep healthcare local. QHR began providing onsite advisory services to Prospect earlier this summer for operational, financial and support functions of the health system until the transaction closes.

"Centurion was created for this exact purpose, to partner alongside providers and communities in creating equitable and cost-effective solutions," said **BEN MINGLE**, Centurion Foundation President. "We believe strongly in the mission of CharterCARE and look forward to the opportunity of engaging in a long-term relationship with the community."

"CharterCARE is excited at the potential of this proposed acquisition, which allows us to build on Prospect's significant investment in Rhode Island healthcare," said **JEFFREY LIEBMAN**, CharterCARE CEO. "The combination of a strong capital partner with an experienced operator of hospitals and the return to nonprofit status is very attractive. We look forward to filing our application with the Department of Health and Attorney General and working with regulators through the review process."

The change in control application process is expected to be submitted to the Health Department and the Attorney General prior to the end of 2022. ❖

Lifespan, Brown, CNE sign agreement to align research operations

PROVIDENCE – Brown University, and Lifespan and the Care New England health systems have signed a new aligned research collaboration (ARC) agreement.

Under the terms of the ARC, the health systems agreed to align their research operations with Brown's Division of Biology and Medicine, which includes the Warren Alpert Medical School, and the Brown University School of Public Health in a unified enterprise that will leverage the distinctive strengths of each institution.

The agreement will help them compete for larger funding opportunities by combining strengths in state-of-the-art research infrastructure, core facilities and specialized equipment. And that cooperative strength will provide new opportunities for clinical trials, allowing Rhode Islanders more access to cutting-edge therapies locally.

The joint approach to research administration will be governed by a Joint Executive Council with representation from all three institutions led by the dean of medicine and biological sciences at Brown. Financially, each institution will continue to support the research enterprise at existing funding levels, and Brown has committed to investing an additional $20 to $25 million once the agreement is fully operationalized.

Establishing the unified operation is intended to spur research programs with high potential to translate into patient therapies and interventions, by strengthening connections between the basic sciences and clinical research. Doing so will accelerate the process of applying discoveries that enhance the detection and treatment of disease, said **DR. MUKESH K. JAIN,** dean of medicine and biological sciences at Brown.

The ARC agreement was developed jointly in recent months and signed in early November. It outlines the formation of a four-member Joint Executive Council that will provide oversight on the organizations' work to unify research operations. The parties agreed to a phased approach to implementing essential elements of the ARC — the agreement marks the first phase and will launch discussions on how to fully operationalize the effort, with the Joint Executive Council ultimately needing to approve separate financial and operational plans before final implementation, expected over the next 12 to 18 months.

The ARC's operational plan will cover topics including research integrity and compliance, institutional review boards and use of research facilities. It will also outline details about research infrastructure, such as staffing for the numerous positions required to operate

While the agreement is not a merger subject to federal or state merger regulations, the organizations are jointly committed to compliance with the strict federal regulations governing research by which each individually abides now. ❖

RI has one of the highest rates of new lung cancer cases according to new report

PROVIDENCE – The 2022 "State of Lung Cancer" report reveals that Rhode Island ranks 43rd in the nation for rate of new lung cancer cases and 1st in the nation for the 5-year survival.

The American Lung Association's 5th annual report, released Nov. 15th, highlights the toll of lung cancer in Rhode Island and examines key indicators including new cases, survival, early diagnosis, surgical treatment, lack of treatment and screening rates.

Nationally, the "State of Lung Cancer" report shows continued progress for lung cancer survival. The lung cancer five-year survival rate is now 25% and increased 21% from 2014 to 2018. Here in Rhode Island, while the rate of new lung cancer cases is higher than the national average, the lung cancer survival rate is the best in the nation at 30.8%.

The report also highlights that people of color who are diagnosed with lung cancer face worse outcomes compared to white Americans, including lower survival rate, less likely to be diagnosed early, less likely to receive surgical treatment and more likely to receive no treatment.

The report found that Rhode Island ranked:

- 43 in the nation for rate of new lung cancer cases at 68.5 per 100,000. The national rate is 56.7 per 100,000.
- 1 in the nation for survival at 30.8%. The national rate of people alive five years after a lung cancer diagnosis is 25%.
- 3 in the nation for early diagnosis at 30.4%. Nationally, only 25.8% of cases are diagnosed at an early stage when the survival rate is much higher.
- 2 in the nation for lung cancer screening at 13.4%. Lung cancer screening with annual low-dose CT scans for those at high risk can reduce the lung cancer death rate by up to 20%. Nationally, only 5.8% of those at high risk were screened.
- 3 in the nation for surgery at 28.3%. Lung cancer can often be treated with surgery if it is diagnosed at an early stage and has not spread. Nationally, 20.8% of cases underwent surgery
- 2 in the nation for lack of treatment at 14%. Nationally, 20.6% of cases receive no treatment. ❖

Lifespan expands collaboration with TriSalus Life Sciences with launch of PERIO-02 clinical trial site

PROVIDENCE – Lifespan and TriSalus Life Sciences, an oncology therapeutics company integrating immunotherapy with disruptive delivery technology to transform the treatment of liver tumors, recently announced the activation of a new PERIO-02 clinical trial site at Rhode Island Hospital.

The opening of the Pressure-Enabled Regional Immuno-Oncology (PERIO-02) clinical trial represents the next phase in Lifespan's partnership with TriSalus following the inception of a separate research laboratory in Lifespan's Coro Building, centered within Providence's Innovation and Design District. The PERIO-02 trial is studying an investigational drug, SD-101, delivered intravascularly by the TriNav® Infusion System using the Pressure-Enabled Drug Delivery™ (PEDD™) method of administration. The study is evaluating whether this platform approach can improve the performance of systemic checkpoint inhibitors in treating patients with HCC or ICC.

"The activation of this clinical trial site and continued collaboration with TriSalus marks an important milestone in our efforts to offer local access to the latest in cancer research," said **MICHAEL HENDERSON, JD, MS, LLM**, vice president for research and chief research officer, Lifespan. "We look forward to building upon this partnership as a leading cancer research center in Rhode Island."

While there have been significant advances in immunotherapy, cancers such as HCC and ICC still present unique treatment challenges, such as immune response suppression and high intratumoral pressure, which can prevent optimal delivery and performance of this class of therapy for patients. The PERIO-02 study, which was first initiated at The University of Texas MD Anderson Cancer Center, is using the TriSalus™ Platform to potentially overcome these delivery challenges and enable more patients with liver and pancreatic tumors to benefit from immunotherapy.

Earlier this year, Lifespan and TriSalus announced the opening of a new on-campus laboratory for conducting immunotherapeutic research, leveraging Lifespan's state-of-the-art vivarium. TriSalus' pre-clinical team, supported by the company's Cranston-based clinical team as well as a grant from the Rhode Island Department of Commerce, is leading research to further develop TriSalus' therapeutic platform and advance medical knowledge of the barriers that can limit the effectiveness of immuno-oncology treatments for patients with liver and pancreatic tumors.

"Expanding the PERIO-02 trial to Lifespan's campus is an exciting addition for both of our teams and, importantly, for patients across New England," said **STEVEN C. KATZ, MD, FACS**, TriSalus Chief Medical Officer. "Broadening our collaboration allows us to go beyond the informative research currently underway to further study our multifaceted approach to potentially improve immune responses for people living with difficult-to-treat cancers."

KHALDOUN ALMHANNA, MD, MPH, serves as principal investigator for the PERIO-02 trial at Rhode Island Hospital. ❖

Appointments

John Fernandez appointed President, CEO at Lifespan

Currently president of Mass Eye and Ear, president of Mass General Brigham Integrated Care

PROVIDENCE – **JOHN FERNANDEZ** has been named the fourth president and chief executive officer of Lifespan, beginning in early 2023. Lifespan's board of directors voted unanimously to approve Fernandez, who is currently president of Mass Eye and Ear and president of Mass General Brigham Integrated Care, both located in Boston, Massachusetts.

Fernandez will succeed Timothy J. Babineau, MD, who stepped down on May 31 after 10 years at the helm.

"These are unprecedented times in healthcare, and we need a transformative leader who has the vision and expertise to guide Lifespan's future strategic direction," said **LAWRENCE A. AUBIN, SR.**, chairman of Lifespan's board of directors. "All the candidates were exceptional and came from major academic medical centers in extremely competitive markets, but John Fernandez stood out as the leader that Lifespan needs during this time."

Aubin added, "I'm confident that John has what it takes to lead Lifespan through the unprecedented headwinds that all healthcare organizations are experiencing across the country. He has demonstrated he is a versatile and engaged leader who can anticipate future possibilities and translate them into breakthrough strategies for Lifespan. John has the ability to mobilize an organization around focused goals and objectives, while also improving employee engagement and the patient experience."

Fernandez will guide Lifespan's strategic direction, build upon its already strong quality and safety program, and focus on Lifespan's ambulatory footprint to make sure patients receive the best possible care in the most appropriate setting. He will continue to work toward better alignment with physicians and to create and foster an environment that advances innovation, transformation, and calculated risk-taking. He will continue Lifespan's work to develop relationships focused on embracing unique patient and community needs and continue to build a diverse and inclusive culture at Lifespan to ensure our employee base is representative of our community.

Fernandez's appointment comes after an extensive national search that was led by a nine-member search committee comprised of board members, physicians, management, and Life-span's community and academic partners including the Warren Alpert Medical School of Brown University. The search committee gathered input from dozens of individuals including senior leaders, employees, physicians, board members, community leaders and other key stakeholders to identify the opportunities and challenges facing Lifespan, as well as the qualifications and leadership competencies for the next president.

About John Fernandez

Presently John Fernandez serves as president of two organizations that are part of the Mass General Brigham healthcare system.

Fernandez is President of Mass Eye and Ear, one of the nation's largest specialty hospitals, exclusively dedicated to academic research, training and treatment for conditions that impair vision, hearing and other disorders of the eyes, ears, nose, throat, head and neck.

Fernandez also serves as President of Mass General Brigham Integrated Care, a Mass General Brigham entity formed in 2019 with a mission to bring lower cost health care closer to where patients live.

Fernandez has excelled throughout his career and has a demonstrated track record of increasing health care options and improving health services. He led key strategic initiatives for Mass General Brigham to provide greater access to ambulatory services in Massachusetts, New Hampshire and other states, including the design, planning, and opening of a multi-specialty ambulatory care and surgical center in Salem, NH.

During his 16-year tenure at Mass Eye and Ear John designed and led a strategic plan that increased surgical volume by more than 70%; grew research funding from $18 million to $72 million; and brought Mass Eye and Ear world-class care closer to patients, by increasing the number of physician office sites from four to 22. John led a $252 million capital campaign to advance science and fund life-changing medical research. In 2018, he executed on a vision for Mass Eye and Ear to become a member hospital of Mass General Brigham.

Prior to his Mass Eye and Ear appointment, Fernandez served as vice president at Brigham and Women's Hospital for several areas including surgical services, imaging, cancer, pathology, laboratory and network development. He is the chair of the Conference of Boston Teaching Hospitals (COBTH) and a member of the Boston Public Health Commission board.

Fernandez received a bachelor's degree in political science from The College of Wooster in Ohio and a master's degree in government administration from the University of Pennsylvania. ❖

Appointments

Physiatrist Ron Avraham, MD, joins pain medicine team at University Orthopedics

EAST PROVIDENCE – University Orthopedics recently announced the addition of board-certified physical medicine & rehabilitation physician **RON AVRAHAM, MD**, who is seeing patients at the practice's Massachusetts locations in Plymouth and Raynham.

While specializing primarily in spinal conditions, Dr. Avraham treats all types of pain. He has comprehensive training and experience performing a number of fluoroscopically-guided spine procedures such as nerve blocks, radiofrequency ablations, and epidural steroid injections to manage and treat neck and low back pain. In addition, he is trained and proficient in the use of ultrasound imaging for musculoskeletal injections including peripheral joints, peripheral nerve blocks, and myofascial and tendon injections including the use of regenerative medicine therapies such as Platelet Rich Plasma (PRP) and Bone Marrow Aspirate Concentrate Stem Cells (BMAC).

Dr. Avraham completed a fellowship training in Interventional Pain at Arizona Pain Treatment Centers in Phoenix, AZ. Prior to that, he received his medical degree from Rutgers New Jersey Medical School in Newark, NJ, then completed his internship in Internal Medicine at Flushing Hospital in Queens, NY, before pursuing residency training in Physical Medicine & Rehabilitation (PM&R) at Temple University/Moss Rehab in Philadelphia, PA. ❖

Brent Emigh, MD, joins Brown Surgical Associates' Division of Trauma and Surgical Critical Care

PROVIDENCE – Brown Surgical Associates today announced it is welcoming fellowship-trained trauma surgeon **BRENT EMIGH, MD** to the practice's Division of Trauma and Surgical Critical Care.

A trauma, burn, acute, and critical care surgeon, Dr. Emigh's professional interests include research in trauma outcomes and value-based care in acute care surgery.

He earned his medical degree from the University College Dublin, Ireland. He completed his residency in general surgery at the Dell Medical School at The University of Texas at Austin. Dr. Emigh went on to complete his fellowship training in trauma surgery and critical care at LAC+USC Medical Center and the University of Southern California. ❖

Timothy D. Murtha, MD, joins Brown Surgical Associates' Division of Surgical Oncology

PROVIDENCE – Brown Surgical Associates recently announced it is welcoming fellowship-trained surgeon **TIMOTHY D. MURTHA, MD, MPH** to the practice's Division of Surgical Oncology.

Specialized in the field of surgical oncology in both the research laboratory and the clinical setting, Dr. Murtha has a particular interest in improving the diagnosis and treatment of malignancies of the pancreas, liver, and biliary system. He has made multiple important contributions to the oncology literature and has published manuscripts that have furthered the field's understanding of pancreatic tumors, melanoma, adrenocortical carcinoma, thyroid cancer, and other diseases.

Dr. Murtha earned his medical degree from Tufts University School of Medicine. He then joined the surgical residency program at Yale School of Medicine where he completed a post-doctoral research fellowship at the Yale Endocrine Neoplasia Laboratory and obtained a Master of Health Science studying the genetic drivers of Adrenocortical Carcinoma. Dr. Murtha went on to round out his training through the Complex General Surgical Oncology Fellowship program at Memorial Sloan Kettering Cancer Center in New York City. ❖

Recognition

Westerly Hospital earns "A" Hospital Safety Grade from Leapfrog Group

WESTERLY – Westerly Hospital has earned an "A" Hospital Safety Grade from The Leapfrog Group in a bi-annual report card released today. This national distinction celebrates Westerly Hospital's achievements in protecting hospital patients from preventable harm and errors.

Westerly Hospital has a long tradition of patient safety. For example, all staff, physicians and volunteers complete "high reliability" training adapted from the aviation and other high-risk industries. This past year, care teams at Westerly Hospital launched and participated in successful initiatives focused on reducing hospital acquired infections and preventing patient falls.

"Providing high quality and safe care to our patients is why we exist," said **PATRICK L. GREEN**, president and CEO, Westerly Hospital. "Our care teams are diligent in their efforts to ensure that we our patients receive the greatest of care in a healing environment that puts safety and quality first."

"To be recognized as an "A' hospital is a great accomplishment for the entire organization it further demonstrates our commitment to improving the health of the communities we so proudly serve," Green added. "When it comes to the health of our patients it matters where they get their care and we are thankful for the trust of the patients and families who choose Westerly Hospital with the knowledge that safety is our top priority."

The Leapfrog Group is an independent national watchdog organization with a 10-year history of assigning letter grades to hospitals throughout the United States, based on a hospital's ability to prevent medical errors and harm to patients. Hospital Safety Grade results are based on more than 30 national performance measures and are updated each fall and spring.

To see Westerly Hospital's full grade details and to access patient tips for staying safe in the hospital, visit Hospital SafetyGrade.org. ❖

Linda Hurley, CODAC CEO, receives 2022 Lifetime Achievement Award from Rhode Island Public Health Association

CRANSTON – CODAC Behavioral Healthcare is proud to announce that **LINDA HURLEY**, CODAC President and CEO, has been awarded the 2022 Lifetime Achievement Award by The Rhode Island Public Health Association, an affiliate of the American Public Health Association. The award was presented at 25th Annual Meeting of The Rhode Island Public Health Association on November 15, 2022, at Rhodes on the Pawtuxet in Cranston, RI.

The award is presented to an individual who has made significant contributions to advance the public's health at a national, state, or local level. Selection criteria is based upon recognition by a group of professionals, public health peers long familiar with the development and advancement of public health in Rhode Island.

Specifically, Linda was recognized for pioneering and leading efforts at the organization, state, and national levels to develop and promote comprehensive, accessible, non-stigmatizing addiction care for all.

Linda has worked in substance abuse treatment and behavioral healthcare for more than 30 years. She has been with CODAC since 1991 and was named CODAC's President/CEO in 2016. Under her leadership, CODAC was the first Opioid Treatment Program (OTP) in the nation to receive Health Home certification and the first OTP in RI to be designated as a Center of Excellence. Furthermore, Linda established a first of its kind comprehensive Medication Assisted Treatment (MAT) Program for corrections in the nation, a recognized Tobacco Cessation program, one of the first HCV treatment programs embedded in an OTP and launched a first in the nation medical mobile unit approved to dispense all three FDA-approved medications for the treatment of OUD. She has been a leader in working to effect policy change in RI, serving on numerous boards and coalitions. Linda has also been called as a consultant for state and federal agencies, including the Substance Abuse and Mental Health Administration (SAMHSA) and the United States Senate. ❖

Obituaries

MAURICE (MAURY) BERMON, MD, 78, of Barrington, RI, passed away Nov. 12th, 2022.

He graduated from the University of Pennsylvania, completed his MD at Tufts University, and his internship at Boston City Hospital (now Boston Medical Center). He completed his residency in psychiatry through Harvard University at Cambridge Hospital.

Maury came to Rhode Island to serve as the Chief of Psychiatry for the Rhode Island Group Health Association, the first HMO in Rhode Island. He worked as a psychiatrist for more than 40 years at RIGHA, Harvard Pilgrim Health Care, Landmark Hospital and finally in private practice. He loved his work and it brought deep meaning to his life.

Since childhood, Maury lived with renal failure and received the gift of life from his brother Stuart, who donated his kidney as a living donor in 1988. Miraculously Stuart's kidney continued to function and sustain Maury for the next 32 years. Maury was predeceased by his brother Stuart in 2007 at the age of 70.

Maury was brilliant, understated, forever curious, and an enduring presence with his family and friends. He loved music of all kinds, especially classical. He was an enthusiastic subscriber to the RI Philharmonic for decades. His children grew up listening to him play Gershwin on the piano. For his entire life he was an avid sports fan and to the surprise of some, a scrappy competitor on the court. He was a lover of food and his friends knew him as a world class eater. He loved to dance and even after two hip surgeries, nothing could keep Maury from the dance floor. More than anything, his family and friends were the world to him.

Maury is survived by the love of his life, his wife, Louise Bermon; his children, David James Bermon (Jessy Needham) of Long Beach, CA, and Susan Elizabeth Stewart-Bermon (wife Becca Stewart-Bermon) of Jamaica Plain, MA, and his niece, Jennifer Bermon, of Marina Del Rey, CA.

Contributions in his honor may be made to Hope Health Hulitar Hospice Center, 1085 N. Main St., Providence, RI 02904, or to Temple Habonim, 165 New Meadow Rd., Barrington, RI 02806. For tributes visit: www.sugarmansinai.com. ❖

ALEXANDER M. CALENDA, MD, 94, of Warwick, died on November 16th. He leaves behind Mary, his wife of almost 62 years, and his children, Giovonne Mary, Alexander, Katherine, and William and his son in-law Scott. He also leaves his dog, Georgie Girl, and kitty, Oliver Twist, whose companionship filled the days with mutual love and joy.

Dr. Calenda was born in Providence on June 17, 1928, the son of Alessandro and Giovannina Calenda, who came to this country as young, Italian immigrants. He was a graduate of Classical High School and Providence College and received a degree in medicine from the University of Bologna, Italy. He completed his internship at St. Elizabeth Hospital and furthered his training at the Harvard University Graduate School of Medicine, receiving a certificate in the Basic Sciences of Ophthalmology. He then completed his residency at Boston University Medical School ,where he served as chief resident. Licensed in RI in 1958 to the practice of medicine, Dr. Calenda proudly maintained his license until his death through ongoing professional development in the field of ophthalmology.

Dr. Calenda opened his private practice in 1960, maintained offices in both Providence and Warwick and was the first ophthalmologist to practice in the Kent County area. He was one of the co-founders of the Department of Ophthalmology at Kent County Hospital and later served as chief of the department. During his career as a surgeon, Dr. Calenda was also on the staff at Rhode Island Hospital and served as Chief of the Department of Ophthalmology at both St. Joseph's Hospital and Our Lady of Fatima Hospital.

Dr. Calenda was board-certified in ophthalmology in 1963, following which he became a Fellow of the American College of Surgeons. He was the first to establish clinical and surgical services at the State Institution and Ladd School, acting as chief medical director at both institutions.

Dr. Calenda was a member of a number of professional associations including the Providence Medical Society, the Rhode Island Medical Society, the American Medical Association, the New England Ophthalmological Society in Boston, MA, the American Society of Ophthalmologists, the Society of Refractive Surgeons, and the New England Ocular Implant Society in Boston, MA.

He was a life-long learner with an inquisitive mind and a desire to know. He valued his own education and instilled this in his children. He was also a teacher who loved sharing his knowledge with others and enthusiastically did so with respect and encouragement. In his later years, he developed an interest in the study of wine and he approached this new passion with almost the same fervor as his medical studies. This led to the founding of The RI Academy of Wine, a collaboration with some of his dearest friends.

Dr. Calenda was also a parishioner of St. Kevin's Church in Warwick and a member of the Warwick Country Club. For all of his experiences and successes it was undoubtedly his love for his family and their love for him that gave Dr. Calenda the most joy and meaning to his life. Nothing compared to the days at Camelot Farm in Warwick Neck. It was the center for many happy celebrations and gatherings with family and friends through the years.

His funeral was held November 22nd at the Thomas & Walter Quinn Funeral Home, Warwick, followed by a mass of Christian burial at St. Kevin Church, Warwick. ❖

CONSTANTINE S. GEORAS, MD, 97, died peacefully at home in Providence on November 12, 2022, surrounded by his loving family.

He was born on June 11,1925 in Bluefield, West Virginia, son of Steve and Anna Georas. When he was five years old, the family moved back to their native Greece, where he was raised and educated. He graduated from the University of Athens Medical School in 1950. When his education was interrupted by the Nazi occupation of Greece in 1941, he joined the Greek resistance movement and participated in strikes, demonstrations, and distribution of supplies in what he described as "a harsh and hungry environment where punishment was swift and ruthless." After his family moved to their homestead in Vraha, Evrytania, he joined the guerilla movement in the rugged mountains of central Greece. He participated in many clandestine operations under the direction of the American Allied Station that was active there during the war.

After graduating medical school, he and his then fiancée, Dr. Venetia (Barbas) Georas came to the United States in 1954, where he completed post-graduate training in New York City and Providence. They were married for 55 years until her death in 2010.

Dr. Georas joined the staff at Rhode Island Hospital in 1956, where he was a practicing cardiologist for more than 40 years. He performed one of the first cardiac catheterizations in Rhode Island, and was an early adopter of echocardiography. He was a beloved physician, dedicated to teaching clinical cardiology to young doctors. He believed in "the triangle made up of enthusiasm, restraint and critical thinking, at the center of which is the patient". He was a Fellow of the American College of Cardiology, and received numerous awards and accolades. In 1993, he received the Irving A. Beck Laureate Award from the American College of Physicians (Rhode Island Chapter) for his abiding commitment to excellence in clinical care and education.

He was a loving husband, father, and pappou (grandfather); he is survived by sister Ouranea Kretsis (of Athens, Greece), daughter Daphne Georas Meredith and son-in-law Steve Meredith (of Jamestown, RI), daughter Lena Georas (of Providence, RI), son Dr. Steve Georas and daughter-in-law Dr. Lisa Beck (of Rochester, NY), six grandchildren, and one great-grandson. He loved nothing more than to spend time with family and friends, and engage in spirited discussions over a good meal. He was a fierce intellect and a compassionate supporter of those less fortunate than he. He remained vital and interested in the world until his final days.

In his memory, please consider a donation to the R.I. Foodbank (rifoodbank.org). ❖

FRANCIS MITCHELL JAMES, MD, of Swansea, MA, passed away peacefully on October 27, 2022 surrounded by his beloved wife Letitia of 61 years and loving family.

Born in Newport, RI, on September 17, 1929, he grew up in Providence, graduating from LaSalle Academy in 1947 and Providence College in 1951.

He graduated from New York Medical College in 1958, followed by an internship at Rhode Island Hospital and Women and Infants Hospital. He proudly served two years in the Navy as a physician on the SS Jason in Japan and then in Coronado. For nearly 40 years, Dr. James dedicated his professional life to his private practice in Obstetrics & Gynecology and believed that taking the time to establish a relationship with each patient was essential to addressing their problems. He was honored to serve as Secretary, Treasurer, Vice President and then President at Charlton Memorial Hospital in Fall River, MA, followed by 12 years as a Trustee. In addition, he was a delegate to the Massachusetts Medical Society and served on the nomination committee.

A long-term member of the New Bedford Yacht Club in South Dartmouth, MA, he cherished time with family and friends on the NBYC cruises and proudly held the title of Fleet Surgeon. He loved all kinds of books, was a voracious reader and was an active member of two book clubs. Equally as important was his love of Opera at the Met, The Boston Ballet and Trinity Theater – always with his bride by his side.

He was predeceased by his parents and his beautiful daughter, Sarah James Garrett. He leaves behind his daughter, Susan James Geremia, her husband Louis Geremia, of Dover, MA, grandchildren, Eliza, Catherine, and Christopher Geremia, son-in-law Dave Garrett (Sandy), grandchild Nathaniel Garrett and several nieces and nephews.

The family wishes to offer their sincere and heartfelt gratitude to his wonderful caregivers for their love, support, and kindness.

A donation in his memory may be made to Doctors without Borders (Doctorswithoutborders.org). For tributes, please visit www.waring-sullivan.com v