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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.

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Inflammatory Bowel Disease in Children and Adolescents

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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

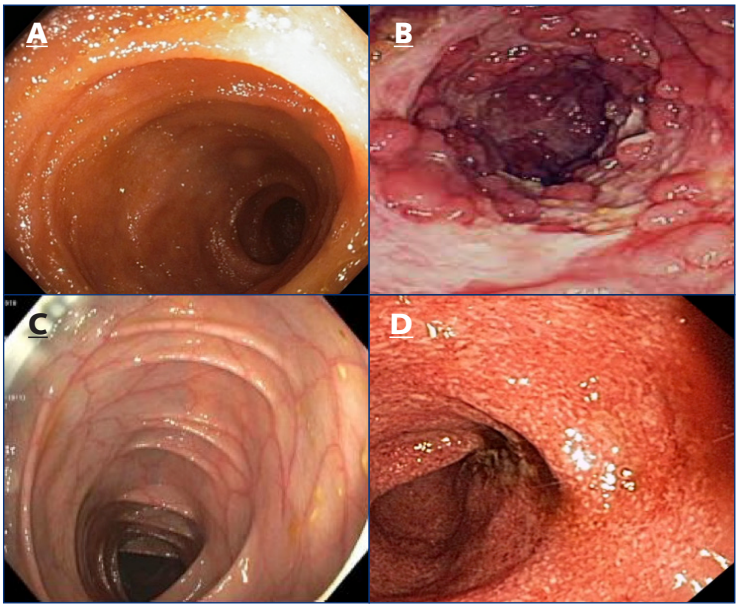
The diagnosis of IBD is based on a combination of clinical, serologic, endoscopic, pathologic and radiographic data. Initial evaluation should involve a thorough history, physical exam and review of outpatient growth charts. Pubertal assessment via Tanner staging should be completed, when appropriate. 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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Approach to Inflammatory Bowel Disease in Pregnancy

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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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Management of the Hospitalized Patient with Acute Colitis

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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.

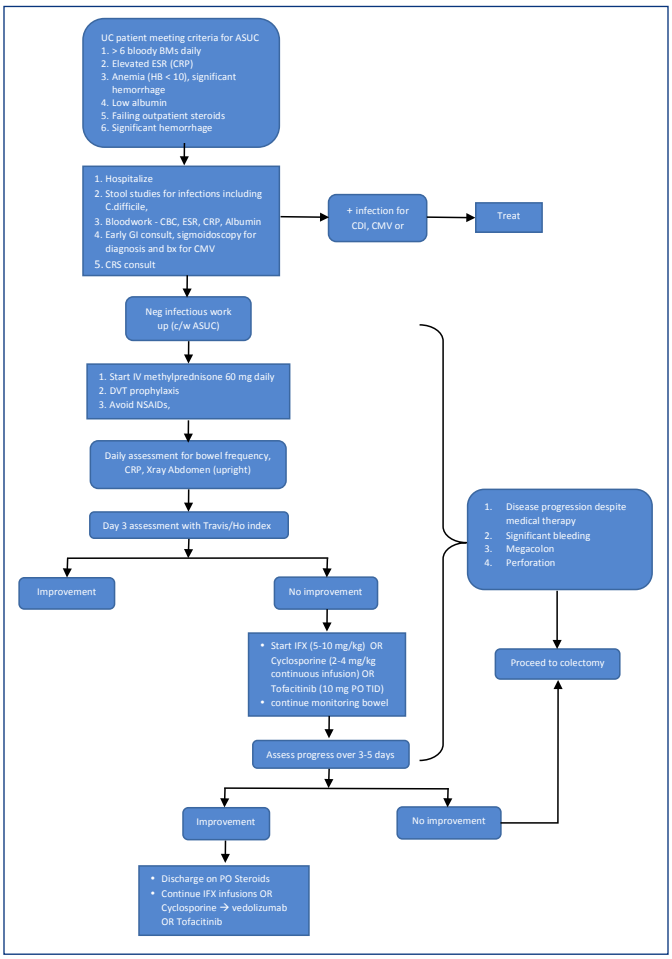
The decision to proceed with surgery is not always as clear as in these emergent situations. Patients failing medical management not having an absolute indication for surgery (perforation, megacolon) will typically benefit from surgery for symptom control. The goal from a surgical standpoint is to operate 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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Surgical Management of Inflammatory Bowel Disease

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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]

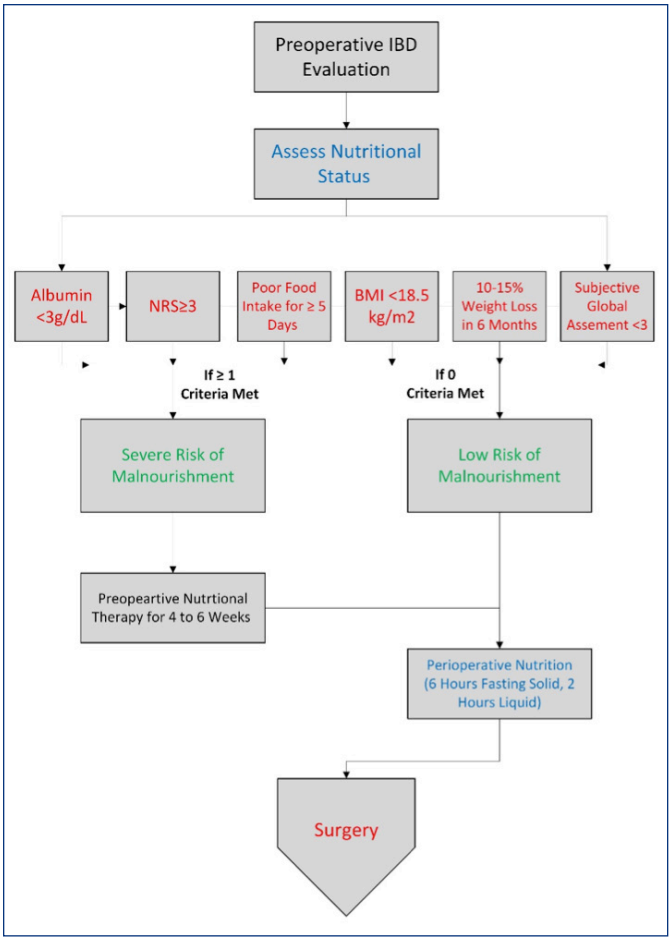
ENHANCED RECOVERY PROTOCOLS

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.

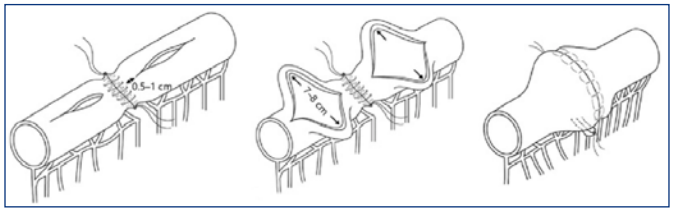
While data on robotic surgery for CD and UC continues to evolve, the current studies that a minimally invasive approach to IBD offers benefits to the patient. The robotic platform presents improved visualization, instrumentation, and dexterity.

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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Nutritional Management of Inflammatory Bowel Disease

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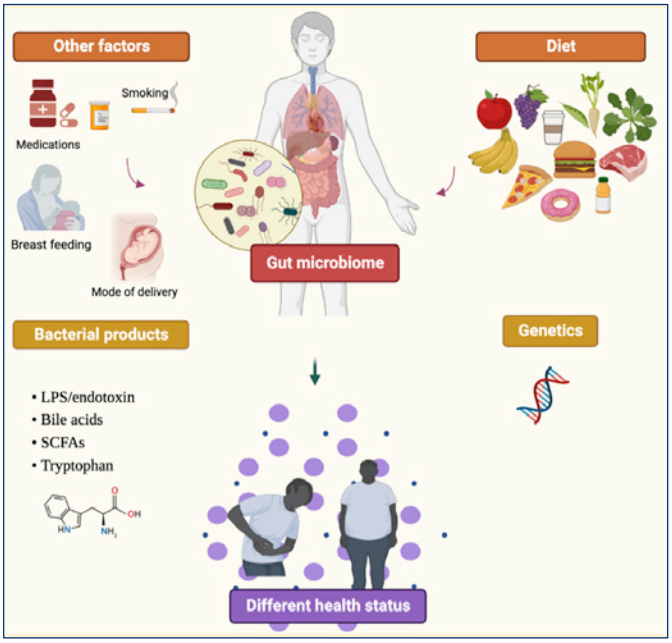
ABSTRACT

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

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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.

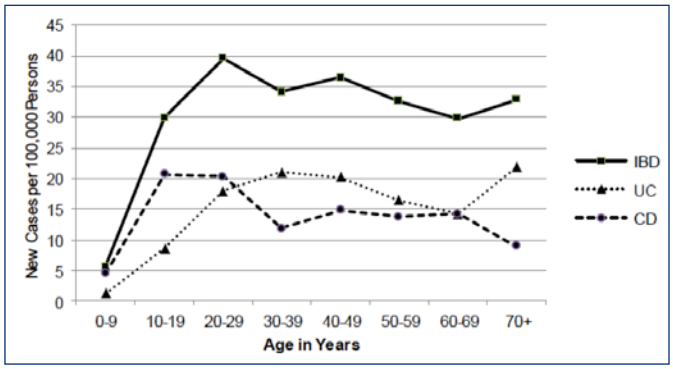
4. Identify clinical and subclinical (including genetic) risk factors for steroid resistance in IBD.

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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Effects of COVID-19 on Patients with Inflammatory Bowel Disease

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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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