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SMALL INTESTINE (D SACHAR, SECTION EDITOR)

The Intestinal Microbiome and Cystic Fibrosis Transmembrane Conductance Regulator Modulators: Emerging Themes in the Management of Gastrointestinal Manifestations of Cystic Fibrosis

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Abstract

Purpose of Review While commonly associated with pulmonary manifestations, cystic fibrosis (CF) is a systemic disease with wide-ranging effects on the gastrointestinal (GI) tract. This article reviews major recent updates in gastroenterological CF care and research.

Recent Findings The high burden of GI symptoms in CF has led to recent studies assessing GI-specific symptom questionnaires and scoring systems. Intestinal dysbiosis potentially contributes to gastrointestinal symptoms in patients with CF and an increased risk of gastrointestinal cancers in CF. An increased incidence of colorectal cancer (CRC) has led to CF-specific CRC screening and surveillance recommendations. Pharmacologic therapies targeting specific cystic fibrosis transmembrane conductance regulator (CFTR) mutations have shown promise in treating GI manifestations of CF.

Summary New research has highlighted the importance of intestinal dysbiosis in CF. Future studies should assess whether CFTR modulators affect the gut microbiome and whether altering the gut microbiome will impact GI symptoms and GI cancer risk.

Keywords Cystic fibrosis · Cystic fibrosis transmembrane conductance regulator · Gastrointestinal microbiome · Dysbiosis · Drug therapy · CFTR modulator

Introduction

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an anion channel expressed in epithelial cells. Mutations in *CFTR* result in impaired Cl^- and $HCO3^-$ transport in the lungs, pancreas, gastrointestinal tract, and sweat glands [1••]. *CFTR* mutations can be classified by the resultant functional defect (Table 1). CF affects approximately 80,000 people worldwide [2]. Although known for its pulmonary complications, cystic fibrosis is associated with a high burden of gastrointestinal (GI) symptoms, and was in fact named for its pancreatic manifestations. Patients with CF commonly report abdominal pain [3] and other GI symptoms [4] which may impact quality of life and treatment adherence.

CF is associated with many gastrointestinal manifestations (Fig. 1). Effects of CFTR dysfunction on the digestive system are evident early and feature prominently. CF mouse models display poor growth and potentially lethal bowel obstruction [5]. CF may present in infancy with gastrointestinal obstruction (meconium ileus), poor digestive function due to inability to neutralize gastric acid, and exocrine pancreatic insufficiency (EPI) leading to nutritional deficiencies and failure to thrive. About 85% of the CF population develops EPI during the first year of life [6]. Pancreatic sufficient patients are at risk for pancreatitis. Although endocrine pancreatic function is relatively preserved early in life, the gradual destruction of islet cells in many patients with CF leads to a high prevalence of cystic fibrosis-related

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Table 1 Classification of *Cystic Fibrosis Transmembrane Conductance Regulator* (*CFTR*) mutations based on functional defect

Mutation Class	I	II	III	IV	V	VI
Defect in CFTR Protein	Functional CFTR is not created	CFTR is misfolded & destroyed so it does not reach cell surface	CFTR reaches cell surface, but channel is less likely to be open due to defective regulation	CFTR reaches cell surface, but chloride conductance is defective	CFTR reaches cell surface, but quantity produced is insufficient	CFTR reaches cell surface, but is less stable
Example mutations	G542X	F508del	G551D	R117H	A455E	Q1412X
	R553X	R560T	V520F	R117C	3849 + 10kbC → T	4326delTC
	W1282X	N1303K	S549R	R334W	2789 + 5G → A	4279insA
Expected exocrine pancreatic status	Insufficient	Insufficient	Insufficient	Sufficient	Sufficient	Insufficient
Targeted drug therapy currently available	None	CFTR Corrector	CFTR Potentiator	CFTR Potentiator	CFTR Corrector, CFTR Potentiator	None

Successful production of functional Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein at the luminal epithelial surface involves multiple steps including transcription of the *CFTR* gene into mRNA in the nucleus, translation of mRNA into CFTR protein and folding of CFTR protein in the endoplasmic reticulum, post-translational modification and packaging into transport vesicles in the Golgi apparatus, and trafficking to the apical membrane of the cell surface. Mutations can occur affecting any of these steps

diabetes (CFRD) in adults. Gastroesophageal reflux, constipation, gastroparesis, cholelithiasis, and small intestinal bacterial overgrowth are common. Potentially life-threatening complications include liver disease and distal intestinal obstruction syndrome (DIOS), in which inspissated stool in the ileocecum leads to bowel obstruction. CF patients have an increased risk for gastrointestinal cancers [7] as detailed below.

The purpose of this review is to highlight topics of current importance in the gastroenterological realm of CF. While not exhaustive, the following topics encompass important recent scholarship or emerging therapies. We will discuss the assessment of GI-specific symptom questionnaires and scoring systems in CF, followed by the potential role of intestinal dysbiosis in GI manifestations of CF. Recent screening recommendations address the increased risk of colon cancer in CF, which likely results in part from intestinal dysbiosis. We will conclude with a discussion of CFTR modulators and their potential role in altering GI symptoms or complications in CF. Figure 1 depicts the themes covered in this literature review and their potential interdependence.

Patient-Reported CF Gastrointestinal Symptom Evaluations

Although often considered primarily a pulmonary disease, CF is associated with a higher burden of GI complications compared to the general population [8]. While the GI manifestations of CF may begin in infancy with the classic presentation of meconium ileus, the development of newer therapies has enabled survival of CF patients well into adulthood—among people with CF born in the United States between 2013 and 2017, half are predicted to live to 44 years old or more [9]. Despite this, the overall burden of CF on GI-specific symptoms and overall quality of life (QOL) is not well understood. A major focus of recent scholarship has been the development of patient-centered systems to quantitatively and qualitatively assess CF-related GI manifestations that have increasingly become chronic diseases of CF.

In one of the first efforts to validate a patient-reported abdominal-specific symptom assessment, Tabori et al. recruited 131 pediatric and adult patients to complete the JenAbdomen-CF Score 1.0, a questionnaire addressing GI symptoms from the preceding three months. Symptoms were grouped into four domains: abdominal pain, non-pain symptoms (e.g. nausea), subjective evaluation of feces' frequency, form, and color, and disorders of eating and appetite [4]. The most commonly reported symptoms were lack of appetite, loss of taste, abdominal pain, flatulence, and distention. The authors also identified 7 conditions which were associated with significantly increased abdominal symptoms: history of rectal prolapse, distal intestinal obstruction syndrome, history of laparotomy, meconium ileus, pancreatic insufficiency, or small bowel resection, and intermittent colonization with *P. aeruginosa*.

Hayee et al. recruited 107 consecutive (i.e. non-selected) patients attending CF specialist appointments to complete pre-existing symptom surveys—the GI Symptom Rating Scale (GSRS); Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) and Cystic Fibrosis Questionnaire-Revised (CFQ-R)—in order to assess the burden of chronic or functional bowel symptoms in CF [10••]. This cohort was comprised of adult patients (mean age 27.8 years), 88% of whom were pancreatic insufficient. Excluding symptoms of

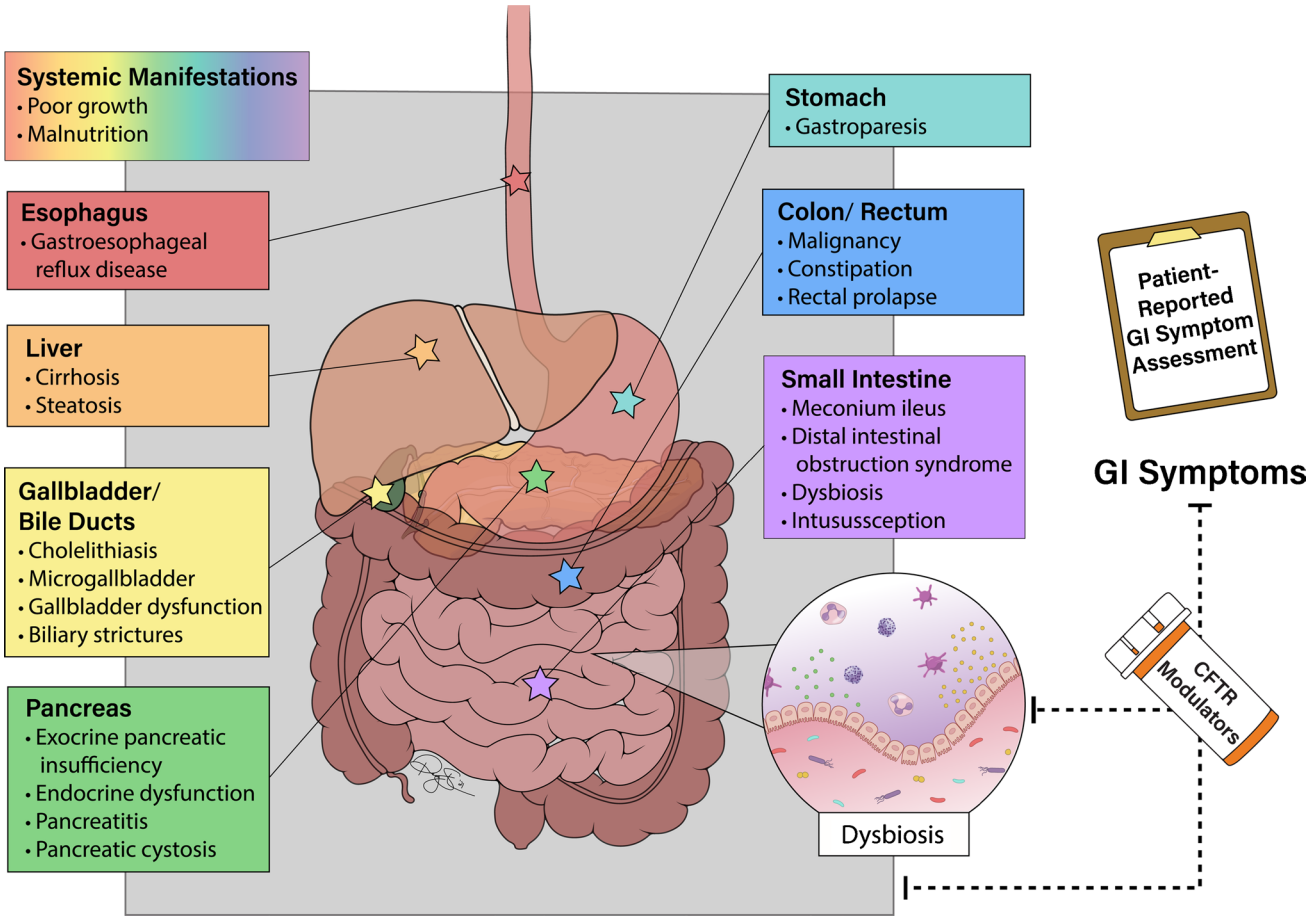

Fig. 1 Potential impact of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators on gastrointestinal manifestations of cystic fibrosis (CF). The boxed panel on the left highlights gastrointestinal complications of cystic fibrosis, grouped primarily by organ. The inset graphic in the lower right represents alterations in the fecal microbiome (dysbiosis). Inhibitory arrows (dashed because they are predominantly theoretical at this time) represent potential effects of CFTR modulators on gastrointestinal symptoms, dysbiosis, and other gastrointestinal complications of CF. GI, Gastrointestinal

pancreatic insufficiency, 65% reported significant GI symptoms. Lower GI tract symptoms (bloating, borbyrygmi, flatulence, and abdominal pain) were most common [10••].

This study suggests that many symptoms reported by CF patients are reminiscent of those seen in IBS. In fact, more CF patients had symptoms that met the Rome IV criteria for IBS than would be expected in the general population [10••]. Of the 2 scales used in the study, a group of patients reported significant symptoms in GSRS but not the SSS, suggesting that the GSRS may be more sensitive for this population [10••]. Due to similarities between CF-related GI symptoms and IBS, it has been posited that some therapies that have proven successful in IBS (e.g. linaclotide for the treatment of IBS-C) may be effective in CF [11].

A multicenter European consortium led by Boon and colleagues integrated a pre-existing GI symptom scale, the Pediatric Quality of Life Inventory, Gastrointestinal Symptoms Scales and Module (PedsQL GI), into a mobile application in order to validate the PedsQL GI in CF [12••]. The PedsQL GI had previously been validated in other pediatric populations (inflammatory bowel disease, gastroesophageal reflux disease, and functional GI disorders), but not in CF [13, 14]. Based on administration of the PedsQL GI in 248 pancreatic insufficient patients with CF age 24 months to 18 years, investigators found that the PedsQL GI was a valid, applicable instrument to assess GI related quality of life (QOL) in children with CF.

A UK-based group evaluated 276 responses to an online survey focused on the impact of gastrointestinal symptoms in cystic fibrosis [15•]. Distributed through online platforms including the Cystic Fibrosis Foundation, the United Kingdom CF Trust, and Twitter, the survey received anonymous responses from CF patients (n = 90), close family/friends (n = 79), and CF healthcare providers (n = 107). Healthcare providers reported that the most common symptoms described by CF patients or their caregivers were reduced

appetite, bloating and constipation, while lay respondents most commonly reported stomach cramps/pain, bloating and a 'combination of symptoms.' Although 94% of healthcare providers felt that pharmacologic therapy helped to relieve GI symptoms, only 58% of lay respondents agreed [15•].

The aforementioned studies illustrate the power of mobile and web-based applications in performing CF symptom assessments, and may facilitate further research using digital platforms to assess CF symptoms. In addition, the Cystic Fibrosis Foundation-sponsored GALAXY study, currently underway, is a multicenter study which utilizes pre-existing patient-reported outcome measures—PAC-SYM, PAGI-SYM, PAC-QOL, and the Bristol Stool scale—with three additional symptom-specific questions [16•]. The GALAXY study aims to assess gastrointestinal symptoms in patients with CF and to develop an objective endpoint for future studies.

The Microbiome in CF

The successful development of Next Generation Sequencing technologies (NGS) has enabled assessment of the relationship between the intestinal microbiome and systemic disease [17]. Knowledge in this arena is rapidly expanding, and it is now widely accepted that the microbiome influences many diseases, including CF, in which mucous accumulation within the GI tract results in abnormal microbial colonization [18].

Multiple recent studies have shown that by infancy, the gut microbiome is altered in CF compared to healthy controls, both in terms of microbial diversity and overall composition [19, 20, 21••, 22, 23, 24]. A functioning pancreas does not seem to affect this dysbiosis [22, 25]. Interestingly, both the lung and gut microbiomes play a crucial role in the expression of CF, and one may influence the other. Madan et al. and Hoen et al. have shown a relationship between the development of the gut and lung microbiomes [26, 27]. Intestinal microbial dysbiosis may be further exacerbated by antibiotic therapy commonly used to treat pulmonary infections in CF [28].

The clinical impact of intestinal dysbiosis in CF is unclear, but a recent body of evidence suggests that it may play a role in disease. Antosca et al. showed a lower predominance of *Bacteroides* spp in CF, a species which they postulate is associated with healthy immune modulation [19]. Burke et al. showed a high prevalence of virulent strains of *C. difficile* in the fecal analysis of asymptomatic adult patients with CF, suggesting that they may play a role in nosocomial transmission of the disease [29]. Small intestinal bacterial overgrowth (SIBO) is thought to affect 30–40% of individuals with CF and is associated with abdominal pain, bloating, flatulence weight loss, and nutrient malabsorption including vitamin B12, iron, bile acids, vitamin D, and folate that consequently can cause anemia [30]. Progressive fecal dysbiosis from birth has been associated with growth failure [31]. Multiple studies have demonstrated higher levels of fecal calprotectin in CF, a marker of gut inflammation derived from neutrophils, suggesting an inflammatory component of CF enteropathy [32–34] that may be influenced by the microbiome. Using 16S rRNA sequencing, Enaud et al. showed similarities between the CF microbiome and Crohn's disease [35]. Finally, Flass et al. demonstrated that compared to CF subjects without liver disease, CF subjects with cirrhosis are more likely to have intestinal mucosal lesions, a relative scarcity of *Bacteroides*, and a relative abundance of *Clostridium*[36].

Probiotics have been used to target CF dysbiosis with varying degrees of success. Systematic reviews have evaluated the clinical use of probiotics in children and adults with CF [37–40•], including a 2020 Cochrane review. The Cochrane review found that probiotics reduced fecal calprotectin, but did not improve overall lung function, growth measures, hospitalizations, or quality of life measures. Adverse events were rare. Results were limited by lack of uniformity of probiotic composition and dosage [40•].

Colorectal Cancer Screening Recommendations

Another consequence of increased longevity in CF has been the revelation that CF patients are at higher risk of GI malignancy than age-matched counterparts. Demonstrated by multiple longitudinal studies [7, 41–43], CF patients have an increased risk of digestive tract cancer, particularly following solid organ transplantation. CF patients appear to have a 5–tenfold increased risk of colon cancer compared with the general population, and advanced adenomas present more frequently and at a younger age [7, 44••]. Mechanisms proposed for this increased risk include the identification of *CFTR* as a tumor suppressor gene [45]. In addition, increased intestinal cell turnover as reflected in elevated fecal M2-pyruvate kinase in children with CF has been postulated as a mechanism [46]. Finally, Dayama et al. [47] evaluated colonic mucosal gene expression and the mucosal microbiome in patients with CF and healthy controls. They reported downregulation of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme in the cyclooxygenase-2 pathway that acts as a tumor suppressor in colorectal neoplasia [48]. Dayama et al. identified patterns of gene expression and alterations in the microbiome that have been previously linked to colorectal cancer. For example, gene expression of *LCN2* was correlated with a paucity of Ruminococcaceae, which is depleted in CRC, while expression of *DUOX2* was correlated with an abundance of *Veillonella*, which was previously identified as a pro-inflammatory bacteria in the CRC microbiome [49].

Based on the increased risk of colon cancer, the Cystic Fibrosis Foundation and the American Gastroenterological

Association (AGA) established a CF colorectal cancer (CRC) screening task force to evaluate available evidence and formulate new CRC screening recommendations in CF. Published in 2018, these CRC screening recommendations are unique to the CF population [44••]. The task force recommends that decisions regarding CRC screening and surveillance be based on shared decision making between the provider and patient, with consideration of treatment, comorbid conditions (e.g. severity of lung disease), safety, and quality of life. The task force recommends CRC screening by colonoscopy (and not by non-endoscopic methods) to begin at age 40 in the non-transplant population and at 30 in those patients who have undergone solid organ transplant. Rescreening is recommended every 5 years in all transplant patients. Surveillance colonoscopy is recommended at 3 years for adenomatous polyps. Finally, it is recommended that all adults undergoing colonoscopy receive intensive bowel preparation regimens.

CFTR Modulators

The most important recent pharmacologic advancements in CF have been the approval of CFTR modulating therapies over the last 10 years. Dubbed a "cause for celebration" by National Institutes of Health (NIH) director Francis Collins, these medications function by targeting specific mutations in *CFTR* [50]. CF is caused by mutations in *CFTR* that affect the quantity of the protein that reaches the cell surface or the function of CFTR channels at the cell surface (Table 1). Unlike previous therapies which sought to alleviate the symptoms of CF, these molecularly targeted therapies treat the mechanism of disease by targeting specific mutations (Tables 1, 2).

The first of these medications, ivacaftor (Vertex Pharmaceuticals, Boston, MA), was approved by the Food and Drug Administration (FDA) in 2012. A so-called "potentiator," ivacaftor potentiates the activity dysfunctioning of gating membranes in the CFTR protein. Ivacaftor primarily targets the G551D *CFTR* missense mutation, present in 4–5% of patients with CF. Ivacaftor has been shown in multiple randomized controlled trials (RCTs) to increase the time that activated CFTR channels at the cell surface remain open, and may lead to significant pulmonary improvement for adult and pediatric patients with the G551D mutation [51–54]. Secondary outcomes from these trials suggest ivacaftor improves nutritional status in both adult and pediatric patients and exocrine pancreatic function (as measured by increasing fecal elastase and decreasing immunoreactive trypsinogen) in pediatric patients [51, 54]. A large follow-up study extending an RCT population of 2–5 year-olds to 84 weeks showed maintenance, but not improvement of, gains made in body mass index (BMI) z scores and pancreatic function during the original 24-week study period [55]. Analysis of combined data from two RCTs including patients age 6 and older with the G551D mutation revealed improved nutritional status at 48 weeks [56].

The most important target of these therapies is the F508del *CFTR* mutation, the most common mutation associated with CF [50]. Although hundreds of different disease-causing *CFTR* mutations have been identified, nearly 90% of individuals with cystic fibrosis have at least one copy of F508del [1••,57]. The F508del mutation leads to a marked reduction in the quantity [1••,58, 59] and quality of CFTR protein at the surface of epithelial cells [1••,58] (Table 1).

Lumacaftor was the first drug to specifically target the F508del mutation, and works by helping to correct F508del CFTR misprocessing and increase the amount of CFTR at the cell surface. FDA approved in 2015 for use in F508del homozygotes aged ≥ 2 years as a combination pill with ivacaftor, lumacaftor-ivacaftor (Vertex Pharmaceuticals, Boston, MA) expanded on the promise shown by ivacaftor alone. As with previous trials that focused primarily on pulmonary outcomes, GI-specific endpoints from large trials are secondary. The TRANSPORT trial, conducted in patients aged 12 or older, demonstrated modest BMI increases at 24 weeks statistically significant compared to placebo [60]. Long-term follow up of these patients to 96 weeks suggests modest but persistent increase in BMI [60, 61]. Despite the success of lumacaftor-ivacaftor, the drug is associated with pulmonary complications including acute pulmonary events such as dyspnea, chest tightness, and a decrease in forced expiratory volume in 1 s (FEV_1) in up to 20% of patients [60, 62–64]. In addition, lumacaftor causes CYP3A4 induction in some patients, leading to prohibitive drug-drug interactions (e.g. inactivation of hormonal contraception) and potentially limiting efficacy of the drug itself [65].

Developed as an alternative to lumacaftor-ivacaftor, tezacaftor as a fixed dose combination with ivacaftor (Vertex Pharmaceuticals, Boston, MA) was FDA approved in 2018 for CF patients 6 or older who are homozygous for the F508del mutation. Like lumacaftor, tezacaftor is a "corrector," and improves processing and trafficking of mutant F508del CFTR proteins. Two large randomized placebo-controlled clinical trials were designed to evaluate the efficacy and safety of tezacaftor-ivacaftor. The first, EVOLVE, was a 24-week trial studying tezacaftor-ivacaftor in patients homozygous for the F508del mutation. The second, EXPAND, was a multicenter, crossover trial evaluating tezacaftor-ivacaftor in patients heterozygous for F508del and a residual function mutation. Although both trials demonstrated improvement in FEV_1, the primary endpoint, neither achieved statistical significance in BMI improvement [66, 67]. Compared to lumacaftor-ivacaftor, tezacaftor-ivacaftor has demonstrated superiority in side-effect profile and medication interactions [68], though concomitant use

Table 2 Currently Approved Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

Medication	Year FDA approved	Mechanism	Indications	GI benefits	Warnings and precautions
Ivacaftor	2012	Ivacaftor potentiates the gating of the CFTR protein at the cell surface, increasing the time that activated CFTR channels remain open	Patients age ≥ 2 years who have one mutation in the *CFTR* gene (primarily G551D) that is responsive to ivacaftor based on clinical and/or in vitro assay data	Modest increase and maintenance of BMI May improve pancreatic function	Elevated liver enzymes; use caution in advanced liver disease Cataracts CYP3A4 Induction
Lumacaftor-Ivacaftor	2015	Lumacaftor improves the misprocessing of F508del-CFTR, resulting in increased amounts of cell-surface protein. See mechanism for ivacaftor above	Patients age ≥ 2 years who are homozygous for the F508del mutation in the *CFTR* gene	Modest increase and maintenance of BMI Observational data suggest decreased hepatobiliary complications May improve pancreatic function and reduce burden of pancreatitis	See ivacaftor Use has been limited by potentially serious acute respiratory events
Tezacaftor-Ivacaftor	2018	Tezacaftor improves the misprocessing of F508del-CFTR, resulting in increased amounts of cell-surface protein. See mechanism for ivacaftor above	Patients age ≥ 12 years who are homozygous for the F508del mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence	Modest increase and maintenance of BMI	See ivacaftor
Elexacaftor–Tezacaftor–Ivacaftor	2019	Elexacaftor and tezacaftor bind to different sites on the CFTR to facilitate increased cellular processing and trafficking of F508del-CFTR to to the cell surface. See mechanism for ivacaftor above	Patients age ≥ 12 years with at least one F508del mutation or at least one other mutation in the *CFTR* gene that is responsive to elaxacaftor- tezacaftor-ivacaftor based on in vitro data and/or clinical evidence	Modest increase and maintenance of BMI	See ivacaftor

FDA, Food and Drug Administration. BMI, Body Mass Index. CYP3A4, Cytochrome P450 3A4

of tezacaftor-ivacaftor with strong CYP3A inducers may require dosage adjustments [68, 69].

With the combination of ivacaftor plus either lumacaftor or tezacaftor, approximately 50% of patients with CF were eligible for CFTR modulating therapy [70]. In 2019, a new triple combination therapy containing ivacaftor, tezacaftor, and the novel drug elexacaftor (Vertex Pharmaceuticals, Boston, MA) was FDA approved for CF patients aged ≥ 12 with at least 1 F508del mutation. Elexacaftor is a CFTR corrector that binds CFTR at a different site than tezacaftor to facilitate processing and trafficking of the CFTR protein to the cell membrane [71]. The concomitant use of elexacaftor, tezacaftor, and ivacaftor improve the function of F508del mutated CFTR protein at the cell surface. The addition of triple combination therapy to the arsenal of CFTR modulators has increased eligibility for CFTR modulating therapy to approximately 90% of CF genotypes [70].

Two trials evaluated the safety and efficacy of elaxacaftor-tezacaftor-ivacaftor combination therapy. The first compared the study drug to tezacaftor-ivacaftor in patients aged ≥ 12 who were homozygous for the F508del mutation. After 4 weeks, those patients in the interventional arm had an absolute improvement of 10% predicted FEV_1 versus the standard of care. While not included as a primary or secondary outcome, the trial noted a 4-week increase in BMI [72••]. The second trial, VX17-445-102 Study, compared the study drug to placebo in a similarly aged population of F508del heterozygotes. At 4 weeks, the interventional group showed a 13.8% absolute increase in predicted FEV_1 versus the standard of care. At 24 weeks, the mean difference in BMI (a secondary outcome) between the interventional group and placebo group was 1.04 kg/m^2, which was statistically significant [1••]. Among gastrointestinal side effects in the second trial, diarrhea was reported in 12.9% of patients in the interventional group versus 7.0% in the placebo group. Use of elexacaftor-tezacaftor-ivacaftor in younger children age 6–11 has also been assessed in a 24-week open-label study which demonstrated safety and efficacy as well as increase in BMI for age z-score over the study period [73].

Notably, all of the CFTR modulators have a risk of elevation of liver enzymes. For patients without pre-existing liver disease or liver function test abnormalities, liver function testing should be performed at baseline, every 3 months during the first year of treatment, and annually thereafter. In addition, dosing should be interrupted in patients with significant elevations of transaminases (e.g., ALT or AST > 5 × upper limit of normal [ULN], or ALT or AST > 3 × ULN with bilirubin > 2 × ULN) and laboratory tests should be closely followed until abnormalities resolve [74]. The manufacturer does not recommend use of elexacaftor-tezacaftor-ivacaftor in Child–Pugh Class B or C liver disease; if used despite the risks in Child–Pugh Class B liver disease, dose adjustment is recommended due to an association with bilirubin elevation in a small clinical study [74]. Patients with pre-existing liver disease or history of liver function test abnormalities may need more frequent lab monitoring. In the VX17-445–102 study, one patient with pre-existing cirrhosis in the interventional arm discontinued the drug due to portal hypertension. [1••] Otherwise, data regarding liver injury linked to these medications is sparse, but more data may emerge as their use increases [75]. Further complicating the picture, elexacaftor inhibits uptake by OATP1B1 and OATP1B3, anion transporting polypeptides expressed in hepatocytes [74]. Since bilirubin is a substrate of OATP1B1 and OATP1B3, one might expect hyperbilirubinemia as a result of this mechanism. Indeed, 5% of patients in the VX17-445–102 study receiving the drug developed hyperbilirubinemia, compared to 1% in the placebo group. [1••]

Most of the data regarding GI outcomes of CFTR modulators come in the form of observational studies and case reports. In addition, because of the recent entry into the market of tezacaftor-ivacaftor and elexacaftor-tezacaftor-ivacaftor, much of the current data assessing GI-specific outcomes of CFTR modulators pertains to ivacaftor and lumacaftor-ivacaftor. However, more data should emerge as investigators begin to evaluate the GI effects of these newer medications.

Lumacaftor and ivacaftor have shown promise in treating CF-related hepatobiliary complications. Though causality cannot be established due to its observational nature, a review of U.S. and U.K. CF registry data indicated that ivacaftor treatment was associated with fewer hepatobiliary complications compared with no CFTR modulator therapy [76, 77]. In a cross-sectional study of 20 subjects with CF, lumacaftor-ivacaftor use was associated with reduced hepatic steatosis (as measured by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) [78]. The drug was also associated with lower total bilirubin. Finally, ivacaftor may help restore disruption of enterohepatic circulation of bile acids in CF patients with S1251N and G551D gating mutations [79].

Lumacaftor and ivacaftor may also improve CF-related pancreatic disease. A small case series suggests that use of ivacaftor may reduce episodes of pancreatitis in pancreatic sufficient CF patients with recurrent pancreatitis [80]. While modest promise has been shown in early markers of CFRD, such as glucose tolerance and insulin response, permanent improvements in CFRD have proven elusive [77, 81–85]. For both ivacaftor alone and lumacaftor-ivacaftor, studies reporting a variety of pancreatic exocrine function outcomes (fecal elastase, lipase supplementation dosage, and serum immunoreactive trypsinogen) suggest improvement of EPI, but limited conclusions can be drawn due to study limitations, including small sample size, lack

of control group, and unknown variability of outcome measures over time [51, 54, 77, 86, 87].

Lumacaftor and ivacaftor may improve additional GI-related illness. Ooi and colleagues evaluated the effects of ivacaftor on fecal calprotectin and intestinal microbial communities (using 16SrRNA variable 3 gene region amplicon sequencing) in 16 patients [88••]. Ivacaftor was associated with an increase in *Akkermansia* spp, and a decrease in *Enterobacteriaceae* which correlated with a decrease in fecal calprotectin. The clinical impact of these findings is not known. Other studies have shown promise in nutritional status [56], extra-esophageal reflux [89], symptomatic celiac disease (CD) in pediatric patients (case series) [90], and proximal small intestine pH profile [91].

Conclusions

As new therapies emerge and patient longevity increases in CF, research has increasingly focused on GI manifestations. Four recent developments provide a major boost to the emerging field of CF gastroenterology. The development of patient-reported GI symptom scoring systems has helped standardize symptom reporting and identify areas for intervention. Studies attempting to characterize the microbiome in CF demonstrate its potential role in GI symptoms and raise the possibility of targeting the microbiome for therapeutic benefit. Recognition of the heightened risk of colorectal cancer in the CF population has led to recommendations for screening colonoscopy beginning at age 40 in the general CF population and 30 in transplant recipients. Finally, CFTR modulators are the first targeted pharmacologic therapies for CF. Because these new medications were originally studied for their impact on pulmonary complications, data regarding their impact on GI manifestations of CF are just beginning to emerge. Future research should assess the impact of CFTR modulators on the gut microbiome, GI symptoms, and GI cancer risk.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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• Of importance
•• Of major importance

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