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Bacterial overgrowth, dysbiosis, inflammation, and dysmotility in the Cystic Fibrosis intestine

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Abstract

Gastrointestinal disease in Cystic Fibrosis (CF) is caused by defective chloride and bicarbonate transport in intestinal cells leading to reduced intraluminal fluidity, increased mucous viscosity and consequently development of intestinal inflammation, dysbiosis and often times dysmotility. This triad is also referred to as the "CF gut". A diagnosis is mainly based on clinical observation and treatment is often times decided empirically. This review of the literature should provide CF caregivers with some tools to identify intestinal inflammation, dysbiosis and dysmotility as possible cause for their patient's gastrointestinal complaints and provide an overview of our current approach to its management.

Keywords: Bacterial overgrowth; SIBO; Dybiosis; Intestinal inflammation; Dysmotility; CF intestine; Probiotics

1. Introduction

Cystic fibrosis is an autosomal recessive disease caused by mutations in the gene that encodes the cystic transmembrane conductance regulator (CFTR) protein. The clinical consequences of this disease are multisystemic, but it predominantly involves the airways and the gastrointestinal track. As the median age of survival in CF increases [1,2], CF patients disproportionally report an increase in gastrointestinal symptoms contributing to their perceived CF disease burden. Meanwhile, studies in CF animal models have helped to gain better insight in the pathophysiology of the CF gut. Recent clinical studies, particularly those reporting about changes in the CF intestine in association with first CFTR-modifying drugs, further helped to put gastrointestinal complications back into the CF clinical focus. The CF gut, similarly to what has been described to happen in CF airways, is subjected to a vicious cycle involving impaired luminal flow due to a highly viscous mucus layer, epithelial inflammation, infection and/or dysbiosis. In this article, we review current literature in regards to the development, diagnosis and management of small intestinal bacterial overgrowth, intestinal dysbiosis, intestinal inflammation, as well as dysmotility in the setting of CF.

2. General background of the CF intestine

The CFTR protein is functionally expressed at the apical membrane of the enterocyte, where it mediates the secretion of chloride and bicarbonate across the epithelial layer. In conjunction with other ion channels and transporters, such as the epithelial sodium channel (ENaC), the sodium-proton exchanger (NHE3) and SLC26A9 (a chloride channel), CFTR is a key player in the intestine to regulate salt and water flux into the intestinal lumen and thus to maintain the fluidity as well as the pH of the luminal contents. Interestingly, the duodenum contains the highest CFTR messenger RNA levels (mRNA) along the intestine, including its mucus-secreting

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Brunner's glands. From there, the mRNA levels progressively decrease to the ileum [3]. Corresponding to this distribution of CFTR, the highest production of bicarbonate is found in the proximal intestine, where it contributes to the dramatic pH switch from the high acid load of the stomach to the alkalinized milieu in the duodenum and proximal jejunum [3]. A high pH environment is essential for the activation of the pancreatic enzymes, micelle formation and fat absorption.

Next to maintaining an adequate luminal pH for nutrient digestion and absorption, luminal secreted bicarbonate is required for normal expansion and solubility of the intestinal mucus [4]. A decrease in bicarbonate leads to an increase in viscosity and impaired mucus propagation through the intestinal tract. In turn thickened mucus serves as an ideal milieu for the colonization of bacteria or also alteration of the normal colonic microbiome and secondary development of chronic inflammation [5].

3. Small intestinal bacterial overgrowth in CF

3.1. Background

In the average human gastrointestinal ecosystem there are approximately 300 to 500 bacterial species (microbiota) that make up a microbiome of nearly 2 million genes [6]. At birth the gut is sterile, but by 2 ½ years of age, the microbiota has reached its final composition, similarly to the one seen in adults [6]. Though some bacteria can be found in the proximal intestine, predominately aerobic species, the overall number is much smaller compared to the large fecal microbiome of the colon [6]. Small intestinal bacterial overgrowth (SIBO) is a disease state in which the bacterial burden in the small intestine exceeds 10 colony-forming units/1 mL in intestinal sampled fluid [6,7].

In CF mice, SIBO occurred within four days of birth [8]. The timing of onset of SIBO in CF patients is less clear. It has been proposed that SIBO in CF individuals is a consequence of the accumulated thickened mucus that acts as an anchor for bacteria, and impairs the normal bacterial defenses provided by the intestinal epithelial Paneth Cells [5]. Furthermore, a high bacterial load itself can induce mucus secretion and thus entertain the vicious cycle of mucus plugs and dysbiosis, as suggested by investigation of mucin gene expression in CF mice [9].

3.2. Clinical presentation

SIBO can lead to diarrhea, abdominal pain, bloating, flatulence and/or weight loss. SIBO can be associated with nutrient malabsorption including vitamin B12, iron, bile acids, vitamin D, and red blood cell folate that consequently can cause anemia [10].

3.3. Diagnostic work-up

Approximately 30–40% of individuals with CF are thought to suffer from SIBO [11–13]. The diagnosis of SIBO is difficult. A direct, but invasive method involves the sampling of bacteria in the small bowel by endoscopic aspiration. In CF, bacteria are likely to be predominantly in the mucus layer, which is poorly soluble and strongly adheres to the intestinal wall. A full evaluation of the bacterial load may therefore require intestinal biopsies in addition to luminal sampling [5]. In contrast, breath testing allows for a non-invasive, but indirect way to assess for SIBO. This test measures exhaled gases produced by bacterial fermentation of an ingested substrate. Most commonly, hydrogen, often combined with methane, is measured following ingestion of lactulose or glucose. However, the metabolism of lactulose may reflect bacterial load in the colon rather than the small intestine [14]. Guidelines for patient preparation and test performance for hydrogen and methane breath testing were published from the Rome Consensus Conference [14–16]. The additional measurement of methane next to hydrogen is particularly important in patients with CF who produce methane more often in SIBO as compared to non-CF controls [16], which may be due to increased mucins in the CF intestine. Also, the frequent antibiotic use in CF may predispose to colonization with mainly methane-producing bacteria. Often times SIBO is associated with intestine dysmotiliy in CF. Delayed intestinal transit may challenge the interpretation of the breath test. Additionally, in CF patients with progressive lung disease, breath tests may be of limited value due to gas retention caused by mucus plugged airways and gas trapping.

3.4. Routine management

Given the limitations of testing for SIBO, empiric treatment is a reasonable approach and is widely practiced. Resolution of clinical symptoms certainly confirms the contribution of SIBO to the symptoms. The therapy for SIBO is based on antibiotics typically directed towards gram negative and anaerobic bacteria. These include metronidazole or rifaximin (a non-absorbable antibiotic drug), which is administered for 10 to 14 days [17], or amoxicillin/clavulanate, which has been shown to stimulate duodenal contractions when given before a meal. This additional effect on intestinal motility may be helpful in individuals with decreased intestinal motility [18]. In adults doxycycline can also be used for SIBO treatment. Antibiotics can be given for a short course interval or for longer duration treatment. In case of the later, it is best to cycle the antibiotics in a 2 weeks on-off regimen, also possibly alternating with a second antibiotic, to decrease the risk of development of bacterial resistance. CF mice which are treated with ciprofloxacin and metronidazole showed significant reductions in inflammation and demonstrated improved weight gain [5]. Interestingly, the use of polyethylene glycol (PEG)-based laxative was equally successful in decreasing bacterial overgrowth by 90% in CF mice [9]. This was also observed in the clinical setting where the use of a daily laxative (PEG 3350 or docusate sodium) as well as inhaled ipratropium decreased the likelihood of a positive breath test in a small group of CF patients [13]. A suggested clinical algorithm for

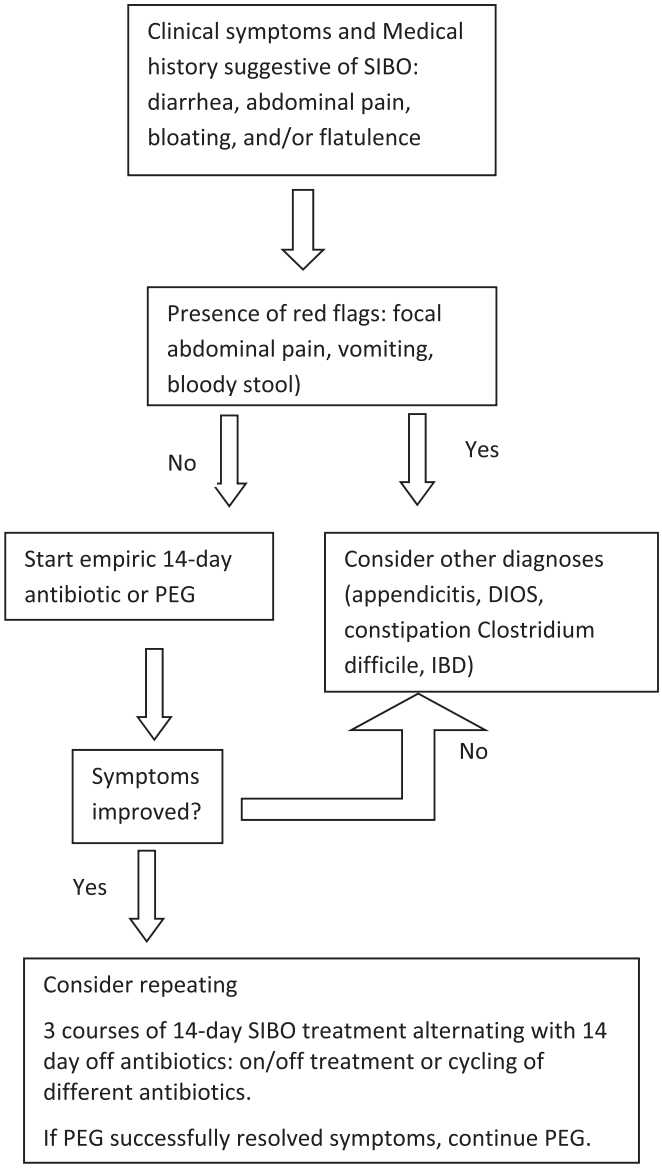

Fig. 1. Diagnostic work-up and management of SIBO.

management of SIBO in CF can be found in Fig. 1. A summary of the drugs used for treatment of SIBO is provided in Table 1.

4. CF intestinal dysbiosis

4.1. Background

Not only are individuals with CF at risk for the development of SIBO, their colonic microbiota is altered as well when compared to individuals without CF. [19,20] Commensal microbiota interacts with the intestine forming a symbiotic relationship. Benefits to the host include bacterial participation in nutrient digestion, upregulation of cytoprotective genes, immunomodulation to protect against potentially pathogenic organisms, and downregulation of inflammation [6]. These benefits are lost with alteration of the commensal microbiota. Dysbiosis in CF can certainly be explained with the altered intestinal milieu of luminal mucus accumulation as well as the high-frequent exposure to antibiotics. However in regards to the latter, recent studies have shown that the antibiotic-induced changes in the microbiome often resolve shortly after the antibiotics are withdrawn; [21,22] though it may not fully recover, but rather establish a new baseline [21].

Repeated exposure to antibiotics does not fully explain the intestinal dysbiosis found in individuals with CF, as already younger CF children demonstrate a higher abundance of the gram-negative bacterium *Escherichia coli* compared to children without CF. [23] Further, Ruminococcus gnavus has been found in patients with CF, but not in their non-CF siblings [24]. The increased mucus found in the gastrointestinal tracts of individuals with CF may preferentially select R. gnavus strains since they are known as mucin degraders. One study showed that there is a substantial decrease in Bifidobacteria; a bacteria which is tightly associated with the development of the immune

Table 1
Medical treatment of SIBO, Intestinal Dysbiosis and Dysmotility.

Medication	Dosing	Treatment
Small bacterial overgrowth		
Metronidazole	Pediatric: 20 mg/kgBW/d ÷ b.i.d. or t.i.d. Adults: 500 mg t.i.d.	10–14 d
Rifaximin	Pediatric: 3–11 years: 200 mg t.i.d ≥12 years: 550 mg t.i.d. Adults: 550 mg t.i.d	10–14 d
Co-trimoxazole (sulfamethoxazole-trimethroprim)	TMP 12 mg/kgBW/d ÷ t.i.d.	10–14 d
Amoxillin/clavulanate	Pediatric: 40 mg/kg BW/d ÷ t.i.d. Adults: 500 mg t.i.d. or 875 mg b.i.d	10–14 d
Dysbiosis (probiotics used in clinical studies)		
Lactobacillus GG 6×10^9	1 capsules (6×10^9)/d	Continuous
Lactobacillus reuteri 10^{10}	5 drops (10^{10})/d	Continuous
Protexin®	1×10^9/d	Continuous
Bio-Plus®	6×10^9 2×/d	Continuous
Gastroparesis		
Domperdione	Pediatric: 0.4–0.8 mg/kgBW/dose t.i.d or 0.3–0.6 mg/kgBW/dose q.i.d (max 30 mg/d) Adult: 10 mg t.i.d.-q.i.d.	Continuous - give before meal times
Metoclopramide	Pediatric: not recommended Adult: 5–10 mg t.i.d.-q.i.d.	Continuous - give before meal times
Erythromycin	Pediatric: 3 mg/kgBW/dose ÷ q.i.d.; maximum dose: 10 mg/kgBW/d or 250 mg Adults: 40–80 (max. 250) mg t.i.d	Give before meal times - maximally for 4 weeks
Azithromycin	Pediatric: 5 mg/kg/day Adults: 400 mg qday	Give before meal times - maximally for 4 weeks

Note that there are currently no recommendation for any specific probiotics. We have just listed the ones that were used in the described studies.

system [25]. CF mice demonstrate an increase in the bacterial load, such as Enterobacter, *Bacteroides fragilis* and Mycobacteria, and a loss of species diversity when compared to their wild-type littermates [5,26].

Furthermore, there are some observations of differences in the degree of dysbiosis among CF patients. Higher levels of *E. coli* and E. biforme were found in homozygous F508del patients and patients who were classified as having severe CF disease. In patients considered having milder disease higher levels of F. prausnitzii, Bifidobacterium, and *E. limosum* were found [27]. Classification into milder and severe CF of this study was limited; nevertheless the observation was quite interesting raising the question whether gradual changes of the intestinal milieu is associated with differences in the CF microbiota. Differences in the microbiota were also observed in CF patients with liver cirrhosis. CF individuals with a diagnosis of severe CF–related liver disease appear to have a lower abundance of Bacteroides and higher abundance of Firmicutes, which was also associated with findings of intestinal inflammation on video capsule endoscopy [28]. There are currently no longitudinal studies assessing changes in the fecal microbiome and development of dysbiosis over time. Two cross-sectional studies reported early onset of dysbiosis in CF children, but provide conflicting results in regards to an increase in the difference of the CF microbiome compared to healthy controls over age [29,30].

C. difficile can be commonly found in stool cultures of CF patients. Most of the CF patients remain asymptomatic and carry only non-toxigenic strains [31]. However, some carry toxigenic strains and still remain asymptomatic or develop severe colitis [32,33]. Use of gastric acid suppression medication and frequent hospitalizations have been thought to play a role in the frequent occurrence of *C. difficile* in the CF population. However, community-acquired *C. difficile* infections causing severe colitis have been described [34].

4.2. Clinical presentation

The clinical symptoms are similar to the ones described above for SIBO. Patients can exhibit signs of abdominal pain and distension, diarrhea and bloating. Intestinal dysbiosis and consequent infection with *C. difficile* can lead to the development of severe, fulminant pancolitis.

4.3. Diagnostic work-up

Stool can be collected for investigations for the presence of *C.difficile* by culture or PCR techniques. Further stool testing should include toxin A and B testing by ELISA [35].

Denaturating gel electrophoresis and high-throughput sequencing of 16S rRNA is used to identify the diversity and quantify the abundance of the fecal microbiome. While this research technique has allowed us to gain new insights in disease-associated alterations of the fecal microbiome, lack of reference ranges and validation does not yet permit to carry these techniques into clinical management.

4.4. Routine management

There has been an increasing interest to treat intestinal dysbiosis with probiotics and two systematic reviews investigated the clinical use of probiotics for CF. According to their results some studies showed that probiotics decreased intestinal inflammation, reduced abdominal pain, and reduced the number of pulmonary exacerbations, but no conclusions were drawn in regard to specific species, strains, or doses of probiotics given that the studies overall were small and of short duration [36,37] The only adverse event that was detected was mild flatulence in three patients from one study [37]. The authors nevertheless pointed out that probiotics should be used with caution in individuals with central venous catheters due to the risk of sepsis [38,39].

Administration of *Lactobacillus rhamnosus* GG (LGG) in a prospective, randomized and blinded study has led to an increase in Bacteroides in the treated children and was associated with a significant reduction in their intestinal inflammation measured by fecal calprotectin [40]. In another CF probiotic study, the administration of a *Lactobacillus reuteri*-based probiotics correlated with improvements in quality of life as determined by the Gastrointestinal Quality of Life Index (GIQLI) [41]. The GIQLI contains questions about a variety of gastrointestinal symptoms like abdominal pain, fullness, difficulty with bowel motions, impact on activities, and emotional impact [42]. This study suggests that a) CF intestinal dysbiosis has a significant impact on gastrointestinal health and b) gastrointestinal health in CF can be improved with probiotics. Until larger randomized, controlled trials are done no recommendation can be given at the current state in regard to probiotics in CF. Table 1 summarizes the probiotics used in this study.

In anticipation that the gut in CF patients will at one point in life have reached a “status quo” in respect to its intestinal milieu, degree of inflammation and intestinal dysbiosis, any treatment targeting intestinal dysbiosis likely needs to be implemented as continuous treatment.

C. difficile infection needs to be treated with antibiotics, either metronidazole or vancomycin for 10–14 days [35]. In severe therapy-refractory cases fecal transplant is now also being considered in CF. [43].

5. CF intestinal inflammation

5.1. Background

CF mice demonstrate intestinal inflammation and upregulation of inflammation-associated genes [44]. Whole gut lavage of the intestine of CF patients showed an increase in inflammatory proteins [45]. Furthermore, findings of an increase in the fatty acid binding protein (I-FABP) in feces from CF patients suggest significant enterocyte damage in the CF gut [46]. Imaging by wireless capsule endoscopy demonstrated high prevalence of small bowel injury in the small bowel of CF patients including villous blunting, mucosal edema, erythema, denuded mucosa and ulcerations. Interestingly, macroscopic evidence of intestinal inflammation was seen in pancreatic insufficiency as well as pancreatic sufficient CF patients [47]. Some centres use non-steroidal anti-inflammatory drugs to treat the chronic pulmonary inflammation in CF patients. In these patients intestinal inflammation could be also caused by chronic NSAID use [48]. As briefly mentioned above an increase in intestinal lesions were also shown in CF patients with CF-liver disease [28].

5.2. Clinical presentation

Intestinal dysbiosis causes and maintains intestinal inflammation and vice versa. Therefore clinical symptoms such as abdominal pain, diarrhea and bloating may not help to distinguish between these two entities. Mild to moderate degree of intestinal inflammation however may remain silent. However, it may well be that the pain-habituated CF patients may not always complain about chronic abdominal pain.

5.3. Diagnostic work-up

Fecal calprotectin is a protein complex derived mostly from neutrophils [49]. It is widely measured in patients with inflammatory bowel disease as an easy, non-invasive and relatively inexpensive marker of colonic -intestinal inflammation [50]. It correlates well with histologic grade of endoscopically assessed mucosal inflammation in patients with inflammatory bowel disease [50].

Fecal calprotectin measured in stool samples is elevated in CF patients, but only in those who are pancreatic insufficient and to a lesser degree compared to patients with inflammatory bowel disease. Interestingly in a study from Dhaliwal et al. the level of fecal calprotectin negatively correlated with the patient’s body weight and height z-scores [51].

5.4. Routine management

To date it remains unclear how, when, or if CF intestinal inflammation should be treated. As SIBO and dysbiosis may be contributory, probiotics may be thought of as an appropriate treatment. In the previously mentioned study by del Campo, as well as in 4 other studies, treatment with probiotics led to a decrease in fecal calprotectin levels [36,37,40,41]. In CF mice, expression of inflammatory genes decreased after treatment with antibiotics suggesting that bacterial overgrowth plays a role in intestinal inflammation [5]. There was no direct association between SIBO and intestinal inflammation when studied in subjects with and without SIBO using the hydrogen-methane breath test [52]. Probiotic intervention studies showed an association between change in the fecal microbiome towards a more healthy composition and reduction in intestinal inflammation markers [52].

There is an ongoing discussion among Gastroenterologists treating CF patients whether to use anti-inflammatory drugs to ameliorate the intestinal inflammation. One retrospective case series presented 6 out of 12 pediatric CF patients with clinical

gastrointestinal symptoms signs of intestinal inflammation following endoscopy who were started on prednisolone and methylprednisolone of the 12 patients were treated with azathioprine, one with methotrexate, two with mesalazine and one with sulfasalazine as steroid sparing agent. The authors report symptom improvement in all treated CF patients and improvement in histological findings in those who underwent repeated endoscopy [53].

6. Dysmotility in CF

6.1. Background

The CF gut is dysmotile. However, the pathophysiology of this phenomenon has not been determined. One plausible explanation is that the smooth muscle function may be directly affected.

In the healthy gut, the migrating motor complex (MMC) helps to clean out the intestinal lumen between meals. This movement of the intestine keeps the bacterial load low by preventing stasis. This would then raise the question of whether absence of CFTR affects smooth muscle function, which then in turn leads to SIBO. CF mice showed normal smooth muscle activity early in the postnatal period suggesting that dysmotility is not a direct effect of defective CFTR. However, when compared to wild-type mouse the circular smooth muscle showed a profound defect in activity and was non-responsive to cholinergic activation. Further experiments in these mice suggested that high expression levels of prostaglandin levels may be causative for the smooth muscle dysfunction. Inhibition of prostaglandin synthesis, but also oral provided laxative restored intestinal motility in these mice [54].

SIBO itself may contribute to dysmotility. Studies in germ-free rats demonstrated a faster small bowel transit compared to those with typical microbial flora. The intestinal transit of the small bowel was increased or decreased by colonization of the bowel with specific species [55]. *Escherichia coli*, which is overabundant in young children with CF, has been shown to slow down the movement of the intestine [9]. Laxative treatment improved the SIBO as well as the intestinal transit time [9].

A frequently occurring clinical phenotype of intestinal dysmotility in CF is delayed gastric emptying (gastroparesis) [56]. Some case series report about a frequency of 60–80% among CF patients, whereas a pooled analysis of a systemic review estimated an incidence of 38% [56–58]. Individuals with CF who have received lung transplantation are at higher risk of gastroparesis and are at higher risk of developing gastric bezoar (concretion of ingested matter) [59]. Vagal nerve injury during surgery may be a contributing factor, but likely the etiology is multifactorial.

6.2. Clinical presentation

Clinical symptoms of delayed gastric emptying include nausea, persistent dyspepsia, vomiting food ingested hours prior, early satiety, postprandial fullness, and abdominal discomfort. The identification and treatment of delayed gastric emptying is important in the CF population because it may negatively impact food intake and thus overall caloric intake. Dysmotility of other parts of the intestine may cause abdominal pain, diarrhea and constipation as well as bloating and flatulence when associated with SIBO.

6.3. Diagnostic workup

The most common method for diagnosing delayed gastric emptying is by gastric emptying scan [60]. This nuclear study involves ingestion of a test meal labeled with a radioactive isotope and reporting of residual tracer remaining in the stomach over the next 4 h. A consensus statement was published in 2008 trying to standardize this test [61]. Since the defect in gastroparesis in CF, similar to Diabetes mellitus, may be due to a dysfunctional migrating motor complex, the typical 90 to 120 min gastric emptying study may be normal and yet the patient has significant gastroparesis. Therefore a gastric emptying scan may not be as sensitive for the diagnosis of gastroparesis in CF patients. In clinical practice, at least in adult CF patients who show an increased frequency in delayed gastric emptying, empiric treatment with a motility agent can be tried. Small and large bowel dysmotility can be assessed using radiopaque marker studies and scintigraphy to capture the transit time through the small intestine and colon. These exams expose patients to radiation and often times provide only limited resolution. There are novel emerging techniques including wireless luminal imaging and recording of transit time using the Pillcam or the Smartpill; latter can also capture the changes in luminal pH. Other new approaches are the 3D-Transit system, which also uses an intestinal traveling capsule, high-resolution manometry using a colonoscope and MRI motility assessment. Investigators developing these newer tests as clinical useful tools are still learning how to interpret the results [62].

6.4. Routine management

Once recognized and diagnosed, delayed gastric emptying needs to be therapeutically addressed. Clinical guidelines recommend small, frequent lower fat and lower dietary fiber meals [63]. However, this approach is not advisable in CF. Patients with CF related diabetes should maximize their glycemic control since improvement in hyperglycemia can improve gastric emptying [64]. Medical treatment can be tried. Metoclopramide, especially in liquid form, has been advocated in the American College of Gastroenterology clinical guidelines as first-line treatment for gastroparesis [64]. However, this medication has not routinely been recommended for prolonged (>12 weeks) use in children in North America due to the extrapyramidal side effects and the risk of permanent tardive dyskinesia (FDA black box warning) [65]. Metoclopramide may nevertheless be used as first line therapy in adult CF patients. In children and adults domperidone can be tried. However, there are no positive studies supporting the use for domperidone, while domperidone also has a FDA black label

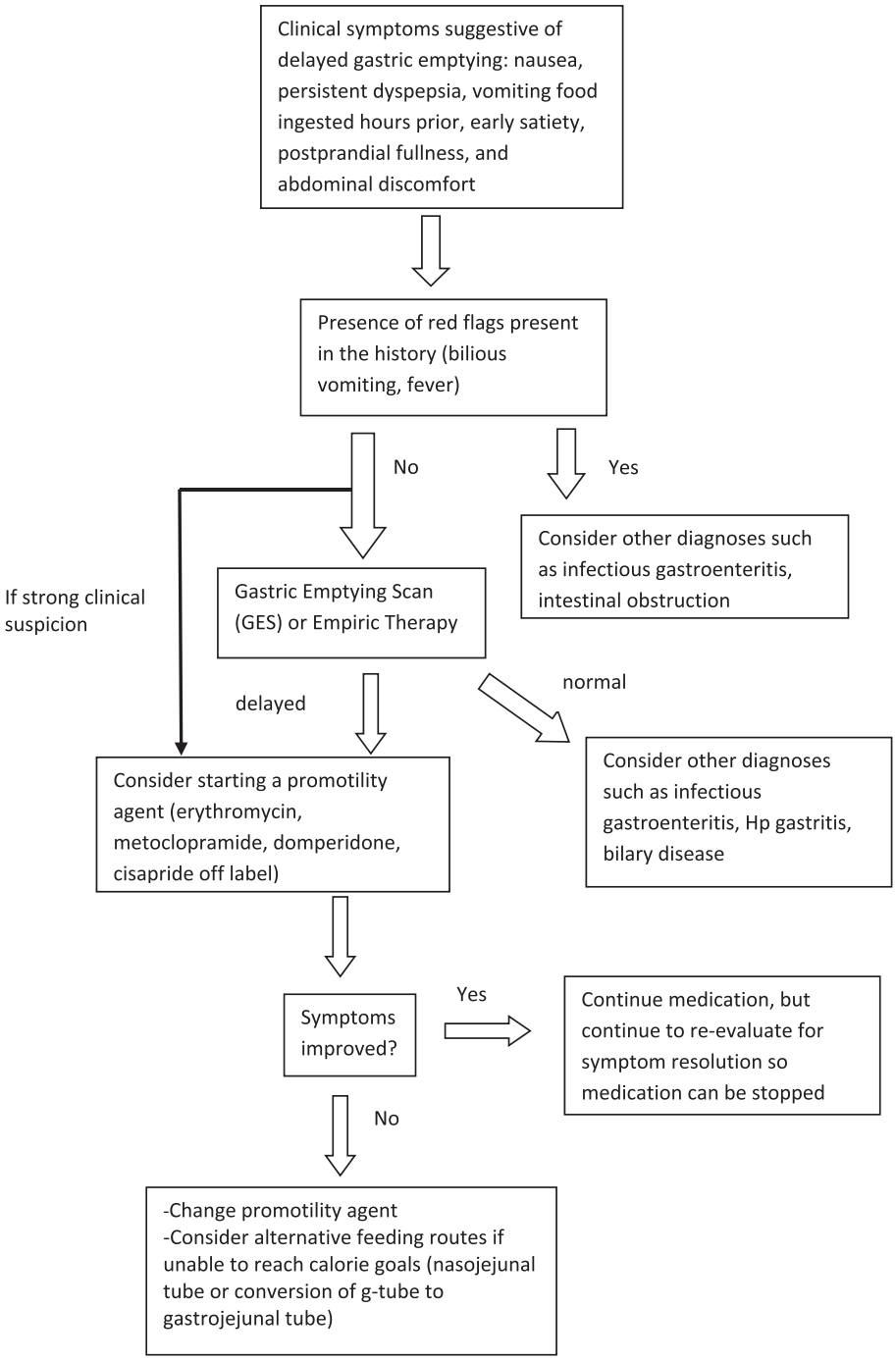

Fig. 2. Diagnostic work-up and management of delayed gastric emptying.

warning of causing cardiac arrhythmias and cardiac death [63,64,66,67]. An electrocardiogram is recommended just prior to and after starting domperidone to ensure absence of a prolonged corrected QT interval; the medication should be withheld or stopped if the corrected QT interval is above the normal reference range [64]. There is mixed evidence for the efficacy of Cisapride, which stimulates release of acetylcholine in the myenteric plexus of the gut and indirectly stimulates motility, in the treatment of gastroparesis [64]. In North America and Europe it has been taken off the market due to an increased frequency of cardiac arrhythmias and death [67]. The macrolides erythromycin and azithromycin, at reduced dosages, are also options in the treatment of gastroparesis due to their better tolerances although they can lead to tachyphylaxis over time [67]. Both of these medications have been shown to be effective in pediatrics and adults [64,67]. Some patients experienced severe GI side effects such as nausea, vomiting and diarrhea. Furthermore, the continuous use of antibiotics may result in dysbiosis or SIBO. Please refer to Table 1 for a summary of the currently used prokinetic drugs.

Regardless of the medical intervention, if the daily caloric goal cannot be met, due to gastroparesis, alternative feeding routes need to be considered, such as gastro-jejunal feeding tubes. A suggested clinical algorithm for addressing gastroparesis in CF can be found in Fig. 2.

6.5. Potential clinical endpoints

Imaging studies such as conventional endoscopy as well as capsule endoscopy [47] may help to document change of visible luminal inflammation following a targeted intervention. Paired analysis of intestinal biopsies or stool for the composition of the fecal microbiome (abundance and diversity) using rigorously validated new gene sequencing techniques may allow conclusion about the efficacy of any targeted therapeutic intervention. In this respect investigations of intervention-induced changes in the fecal metabelome using new mass spectrometry techniques may probably provide a more clinical –relevant read-out of the changes in CF intestinal dysbiosis. Intestinal biomarkers of inflammation, such as fecal calprotectin are already being used as a clinical read-out marker for therapeutic intervention [40].

6.6. Future directions

There are still many open questions in regard to SIBO, dysbiosis, intestinal inflammation, and dysmotility, particularly in regards to the interplay of these components, which as a sum leads to the development of the "CF gut". Large randomized, controlled interventional trials addressing these issues are missing.

Similarly to other gastrointestinal disease, homeostasis of a healthy microbiome seems to be a key regulator of gut health in CF. Disturbance of this ecosystem by a severely altered intestinal milieu (viscous and acidic), frequent use of antibiotics and altered intestinal transit, may contribute to many gastrointestinal symptoms in CF patients. Studies in CF mice have provided some clues about the pathophysiology as well as the possible therapeutic approaches for intestinal inflammation and dysbiosis.

Nutrition is another factor that impacts the fecal microbiome. Nutritional supplements and the often times high caloric, fatty and processed food-based CF diet may cause additional impairment of the CF dysbiosis. Researchers have started investigating the impact of specific diets on the microbiota and Hoen, et al. have found that infants receiving breast milk had a trend towards prolonged time to first CF exacerbation [68].

Newer GI drugs on the market such as Lubiprostone, Linaclotide, both new intestinal secretagogues approved for IBS constipation, or Prucalopride, a new motility agent, may be of benefit to CF patients, but require more rigorous studies to generate the necessary clinical evidence [69–72]. Lastly, newly emerging CFTR-modifying drugs have a direct impact on the intestinal health in CF patients. Initial studies have demonstrated an immediate drug effect on the intestinal pH [73], as well as on the intestinal inflammation [74], which possibly has contributed to the dramatic improvement in the nutrition status in drug-treated patients [73,75,76].

7. Summary

Gastrointestinal disease in patients with cystic fibrosis include small bacterial overgrowth, intestinal dysbiosis, intestinal inflammation and dysmotility. All these single factors are interrelated and significantly contribute to the disease morbidity, especially with increasing patient survival. So far, little is known about how best to diagnose and manage these intestinal disease complications. New investigational technologies, such as e.g. tools to analyze the gut microbiome and disease phenotyping using patient derived organoids as well as novel possibilities of pharmacological intervention provide an opportunity to increase our knowledge in this field in the future.

Conflict of interest

JD declares no conflict of interest; TG receives research grant support from Vertex Pharmaceutical Inc.

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