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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