Conclusions: We found that digestion of powdered milk and CF meconium by pancreatic enzymes was faster with lower salt concentrations. Endogenous pancreatic enzymes are insufficient in patients with MI, and hyperosmolar solutions could slow meconium digestion. Future studies are needed to establish ideal conditions for dissolving obstructive meconium in animal models, with the goal of relieving intestinal obstruction in newborns with MI.

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References

[1] Sathe M, Houwen R. Meconium ileus in cystic fibrosis. *J Cyst Fibros* 2017;16: S32–9.
[2] Escobar MA, Grosfeld JL, Burdick JJ, Powell RL, Jay CL, Wait AD, *et al.* Surgical considerations in cystic fibrosis: A 32-year evaluation of outcomes. *Surgery* 2005;138(4):560–71; discussion 571–2.

191

Cystic fibrosis transmembrane conductance regulator potentiator (ivacaftor) has minimal effects on gut microbiome composition in people with cystic fibrosis and gating mutations

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Background: Cystic fibrosis (CF) is associated with gut microbiota dysbiosis. It is likely that the etiology of microbiota differences in CF is multifactorial and includes impaired bicarbonate secretion, low pH, abnormal gastrointestinal motility, inspissated intestinal stool and mucous, fat malabsorption, lack of endogenous pancreatic enzymes, high fat diet, and frequent antibiotic use. Prior studies have demonstrated altered microbiota composition in individuals with CF. The impact of highly effective CF transmembrane conductance regulator (CFTR) modulator therapy on the microbiota is largely unknown. We compare microbiota composition in individuals with CF and gating mutations at baseline and 3 months after initiation of the CFTR potentiator ivacaftor with that in healthy controls.
Methods: Subjects with gating mutations were recruited from CF centers in the United States and Italy. Stool samples were collected at baseline and 3 months after initiation of ivacaftor treatment. Age-matched healthy subjects were included from two previously published cohorts [1,2]. Microbiome composition was assessed using shotgun metagenomic sequencing with the DNeasy PowerSoil Kit (Qiagen, Germantown, MD) for extraction, the NexteraXT DNA Library Preparation Kit (Illumina, San Diego, CA), and an Illumina HiSeq 2500 using 2 × 125 base pair chemistry. Data were processed using the Sunbeam, abundance of bacteria was estimated using Kraken, and analysis was conducted in R. Dysbiosis score was calculated as the median Bray-Curtis distance to healthy participants.
Results: Eighteen individuals with CF (7 male, 11 female, median age 15.3), 13 of whom had exocrine pancreatic insufficiency and five of whom had pancreatic sufficiency, completed the study. There were no differences in alpha diversity between healthy and CF subjects using richness or Shannon's index, but CF subjects had higher dysbiosis scores ($p < 0.001$) and a different microbiota composition (beta diversity) than healthy controls (Figure 1, permutational multivariate analysis of variance $p < 0.01$). These differences in composition corresponded to a greater relative abundance of *Enterobacteriaceae*, *Escherichia coli*, and *Veillonella parvula* in subjects with CF and a smaller relative abundance in ten *Bacteroidetes* taxa, *Eubacterium rectale, Faecalibacterium prausnitzii,* and *Akkermansia muciniphila* (all false discovery rate < 0.05). By contrast, treatment with ivacaftor for 3 months did not lead to statistically significant differences in alpha diversity (richness or Shannon's diversity index), beta diversity (Bray-Curtis distances), or relative abundance of specific bacterial taxa.
Conclusions: Different microbiome composition was found in subjects with CF than in healthy participants, consistent with previously reported results. We observed no statistically significant effects of ivacaftor treatment on gut microbiota composition, although this was a small cohort with multiple confounders, including antibiotics use and differences in exocrine pancreatic function.

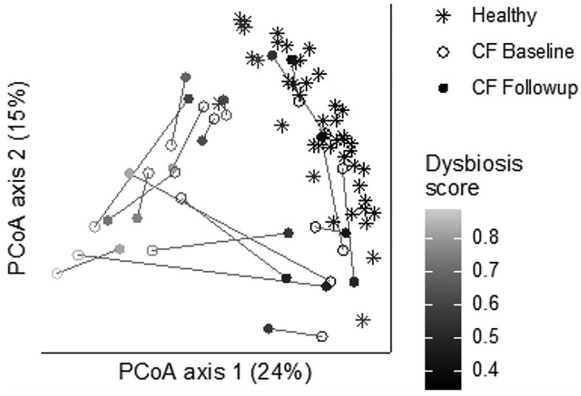

Figure 1. Principal coordinate analysis plot of microbiome composition (Bray-Curtis distance) in people with cystic fibrosis (CF) and healthy controls

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References

[1] Bushman FD, Conrad M, Ren Y, Zhao C, Gu C, Petucci C, *et al.* Multi-omic analysis of the interaction between Clostridioides difficile infection and pediatric inflammatory bowel disease. *Cell Host Microbe* 2020;28(3):422–33.e7.
[2] Tanes C, Bittinger K, Gao Y, Friedman ES, Nessel L, Roy Paladhi U, *et al.* Role of dietary fiber in the recovery of the human gut microbiome and its metabolome. *Cell Host Microbe* 2021;29 (3):394–407.e5.

192

Gastrointestinal symptoms in a cystic fibrosis transmembrane conductance regulator modulator era—an international survey

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Background: How to relieve gastrointestinal (GI) symptoms in people with cystic fibrosis (CF) was identified as a research priority and explored through an international qualitative survey in the CF community in 2018 [1]. After introduction of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in 2019, many more people with CF (PwCF) are able to access CF transmembrane conductance regulator (CFTR) modulator therapy. Although the respiratory benefits of ELX/TEZ/IVA are well documented, effects on the GI tract are not well understood. The aim of this study was to characterize GI symptoms in the CF population and ascertain whether the introduction of modulators affected them.
Methods: PwCF, families, and health care professionals (HCPs) completed electronic surveys over a 1-month period. The survey was promoted

through online forums such as Twitter using the twitter handles @CFAware, @questionCF, and @CARDSCFresearch; Facebook; and professional networks. Ethical approval was gained from the University of Nottingham ethics committee. This analysis presents a summary of the closed questions, with thematic analysis ongoing and performed using NVivo software.

Results: There were 164 respondents from 11 countries, with 85% of respondents from the United Kingdon. One hundred ten respondents (67%) were from the lay community (PwCF 54%, parent 12%, other relative 1%). HCPs (n = 54, 33%) were represented by 10 professional groups, with dietitians the largest professional group (44%). Most PwCF were on a CFTR modulator (n = 89, 81%), mostly commonly ELX/TEZ/IVA.

Most respondents from the lay community (84/95, 88%) and HCPs (33/35, 94%) felt that GI symptoms affected quality of life (QoL) for PwCF. Of those not on a CFTR modulator, 53% (10/19) missed school or work because of their GI symptoms, versus 27% (20/75) on a CFTR modulator. The most common GI symptoms, experienced at least once a week or more regardless of modulator status, were gas and rumbling noises in the stomach and loose bowel movements (CFTR modulator group) and bloating (no modulator group). Symptoms that PwCF most commonly reported as improved since starting a modulator were stomach pain or discomfort (n = 29, 38%), bloating (n = 28, 37%) and loose bowel movements (n = 28, 37%) (scale: worse, same, better, N/A), although stomach cramps and bloating were still identified as the symptoms most affecting QoL in both groups. HCPs reported the most common symptoms affecting QoL for PwCF as being stomach pain, bloating, and diarrhea and constipation. Symptoms that most commonly improved after CFTR modulator use were appetite (26/34, 77%), stomach pain and discomfort (21/34, 62%), and stools that float (18/33, 55%).

Conclusions: Although CFTR modulators have decreased GI symptoms for some PwCF, this survey demonstrates that GI symptom response varies and that GI symptoms continue to be a problem for PwCF regardless of their modulator status and to affect their QoL. Improvements that the lay community reported were different from those that HCPs reported. Understanding GI symptoms remains a relevant research question and a better understanding of the physiology underlying them needs to be further explored.

Reference

[1] Smith S, Rowbotham N, Davies G, Gathercole K, Collins SJ, Elliott Z, *et al.* How can we relieve gastrointestinal symptoms in people with cystic fibrosis? An international qualitative survey. *BMJ Open Respir Res* 2020;7(1):e000614.

193

Association between cystic fibrosis–related liver disease, mortality, and disease burden in children

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Background: Cystic fibrosis (CF)-related liver disease (CFLD) is the third-leading cause of mortality in CF after end-stage pulmonary disease and lung transplant–related complications. CFLD is increasingly recognized because of advancing CF management and greater awareness of clinicians. There is a lack of population-level data on the prevalence and impact of CFLD on mortality and hospital outcomes. The aim of this study is to evaluate the mortality and disease burden associated with CFLD in children.

Methods: We analyzed all people with CF enrolled in any of the 50 children's hospitals participating in the Children's Hospital Association (CHA). We interrogated the Pediatric Health Information System database

Table 1 (abstract 193):
Demographic and comorbidity profile of patients with cystic fibrosis (CF).

Demographics	CF with Liver Disease N= 1,399	CF without Liver Disease N= 20,428	P value
Age (Mean ± SD)	14.7±5.3	10.6±6.7	<0.001
Gender			<0.001
Male	785 (56.1 %)	10466 (51.2%)	
Female	614 (43.9%)	9962 (48.8%)	
Race and Ethnicity			<0.001
Caucasian	956 (68.4%)	136891 (68%)	
African American	55 (3.9%)	1368 (6.7%)	
Hispanic	201 (14.4%)	2111 (10.3%)	
Other	187 (13.4%)	3583 (15%)	
Insurance			<0.001
Public	555 (39.7%)	6503(31.8%)	
Private	457 (32.7%)	7181 (35.2%)	
Self-pay/uninsured/others	387 (27.7%)	6744 (33%)	
Median house hold income	49050±18250	49222±19556	0.72
Chronic respiratory failure	196 (14%)	1000 (4.9%)	<0.001
Intensive care unit admission	655 (47.5%)	3202 (15.7%)	<0.001
Mechanical ventilation	513 (36.7%)	2476 (12.1%)	<0.001
Pulmonary hypertension	48 (3.4%)	201 (1%)	<0.001
Lung transplant	59 (3.3%)	139 (0.7%)	<0.001
Diabetes mellitus	382 (27.3%)	1534 (7.5%)	<0.001
Malnutrition	622 (44.5%)	3619 (17.7%)	<0.001
Need for parenteral nutrition	568 (40.6%)	2616 (12.8%)	<0.001
Malignancies	74 (5.3%)	424 (2.1%)	<0.001
Mortality	136 (9.7%)	457 (2.2%)	<0.001