of CHA to include all people younger than 21 diagnosed with CF using International Classification of Diseases (ICD) diagnostic codes. We defined CFLD as a concomitant diagnosis of at least one of cirrhosis, liver fibrosis, chronic liver disease, esophageal or gastric varices, ascites, portal hypertension, liver transplant, and hypersplenism. People with CFLD were then compared with people with CF without any of these concomitant diagnoses for demographic characteristics and other comorbid conditions. The primary outcome variable was mortality.

Results: We analyzed 21,827 individuals between 2004 and 2021. The prevalence of CFLD (6.4%, $n = 1{,}399$) (Table 1) increased with age, with a peak rate of 16.7% at age 21 ($p < 0.01$). Children with CFLD were older (median 14.7 vs 10.6), and CFLD was more prevalent in boys ($p < 0.001$). Children with CFLD had a greater prevalence of significant comorbidities such as respiratory failure, admission to intensive care unit, mechanical ventilation, pulmonary hypertension, lung transplantation, diabetes mellitus, malnutrition, greater need for parenteral nutrition, and malignancy ($p < 0.001$). After adjusting for various factors, the multivariate regression model showed that CFLD was associated with a 1.7 times greater risk of mortality (95% CI, 1.3–2.2, $p < 0.001$).

Conclusions: CFLD is associated with greater risk of mortality and with multiple comorbidities indicating greater disease severity. Prospective longitudinal studies are required to further delineate the impact of CFLD on children with CF.

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Building an in vitro model to investigate microbial dynamics in the cystic fibrosis gut

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Background: Stability and diversity of the infant gut microbiome are essential for healthy digestion, immune development, metabolism, and protection from infection. Dysbiosis of the intestinal microbiota at a young age has been correlated with poor health outcomes, including metabolic disorders, allergy, and inflammatory diseases. In the context of cystic fibrosis (CF), infants as young as 6 weeks old exhibit gut microbial dysbiosis according to analysis of stool. One signature of this dysbiosis is a significant depletion of a key gut microbe, *Bacteroides*, as well as enrichment of *Escherichia coli*. The goal of this study is to understand the potential mechanism(s) of *Bacteroides* depletion in the infant CF gut. Our central hypothesis was that the environment of the CF intestine and microbial competition with *E. coli*, both of which contribute to significant shifts in metabolic function of the microbiome and, ultimately, overall negative health outcomes, drive the observed paucity of *Bacteroides* in the CF gut at least in part.

Methods: To test the hypothesis that the CF intestinal environment contributes to microbial dysbiosis, we are developing a novel in vitro CF gut medium that uses an established gut microbiome medium, MiPro, supplemented with a variety of factors reported to be differentially abundant in the CF gut: fat, oxidative stress, inflammatory markers, nitrate, sulfate, pH, bile salts, antibiotics, and mucin (Figure 1). We culture clinical isolates of *Bacteroides* and *E. coli* in each component of this medium to examine which physiological features may be modulating microbial viability. To test the hypothesis that the *Bacteroides–E. coli* interaction contributes to *Bacteroides* depletion, we use a co-culture model system consisting of CF clinical isolates of both microbes inoculated at equal densities. After competition (48–72 hours) in both media, we compare the growth and survival of each microbe in competition with that of its monoculture control.

Results: Preliminary results reveal that *E. coli* isolates can kill *Bacteroides* in co-culture and that specific features of the CF gut environment modulate growth and survival of *Bacteroides* in a dose-dependent manner. Under CF and healthy conditions, *E. coli* growth is unaffected. When in co-culture with *E. coli*, *Bacteroides* depletion is exacerbated in the presence of glycerol, probably because of shifts in metabolism by both microbes. In addition, because of *E. coli*'s catalase activity, growth of *Bacteroides* is rescued when hydrogen peroxide is present.

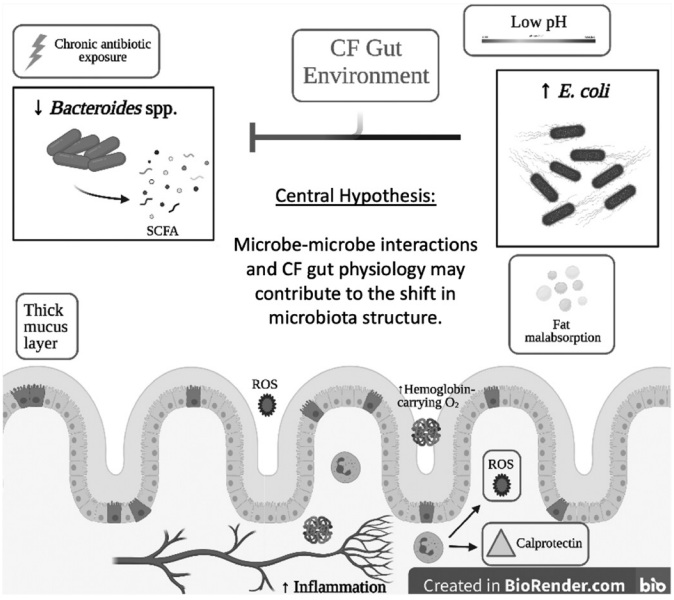

Figure 1. Schematic model of the intralumenal gastrointestinal tract of individuals with cystic fibrosis (CF). In CF, a variety of environmental and physiological factors (red, round-cornered boxes) contribute to loss of *Bacteroides* and an increase in *Escherichia coli*, which is negatively associated with health. We test the central hypothesis that microbe-microbe interactions and CF gut physiology contribute to the observed shift in microbiota structure.

Conclusions: We have been able to identify physiological factors of the CF gut that may drive microbial dysbiosis, with a focus on the immune-training microbe *Bacteroides*. We are concomitantly developing a new in vitro CF gut medium that will allow us, for the first time, to investigate the microbial dynamics of this system. Elucidation of putative causes of microbial dysbiosis will provide insight into effective interventions that may be used to ameliorate or prevent adverse health outcomes in children with CF.

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Impact of elexacaftor/tezacaftor/ivacaftor on serum markers of fat-soluble vitamin levels in people with cystic fibrosis

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Background: The advent of highly effective modulator therapy (HEMT), including ivacaftor and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), has revolutionized the care of most people with cystic fibrosis (PwCF). Less is known about the effectiveness of HEMT in treating extra-pulmonary manifestations, including vitamin malabsorption. The purpose of this study is to evaluate the impact of ELX/TEZ/IVA on serum markers of fat-soluble vitamin levels, specifically vitamins A, D, and E, and prothrombin time (PT, a marker for vitamin K), in PwCF aged 12 and older followed at two large CF centers (one pediatric, one adult) in Seattle, Washington. This abstract describes the results for the pediatric participants.

Methods: In this retrospective cohort study, participants aged 12 and older on ELX/TEZ/IVA were identified through chart review, and information on demographic characteristics, medications, comorbidities, and vitamin levels was collected. ELX/TEZ/IVA start date was obtained from clinic progress notes. The 2 years before ELX/TEZ/IVA initiation and up to 2 years