

## ORIGINAL ARTICLE

## Gastroenterology

# Impact of acid blocker therapy on growth, gut microbiome, and lung disease in young children with cystic fibrosis

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## Abstract

**Objective:** Acid blocker therapy (ABT) has become common in cystic fibrosis (CF), despite insufficient evidence for benefits and studies showing potentially negative effects. We examined associations between ABT usage and growth, gut microbiome (GM), and early-onset lung disease in young children with CF.

**Methods:** One hundred and forty-five infants with CF born during 2012–2017, diagnosed through newborn screening by age 3 months and followed to 36 months of age at six CF centers were evaluated. Longitudinal data on growth, pancreatic functional status, pulmonary symptoms, and acid blocker medications were prospectively collected. Early-onset lung disease severity was evaluated by a clinical scoring system. GM composition was assessed by 16S rRNA methodology.

**Results:** ABT use before age 3 years was frequent, with 81 (56%) of patients on H2 receptor antagonist (H2RA) or proton pump inhibitor (PPI), and higher among pancreatic insufficient (60%) versus pancreatic sufficient (26%) children. H2RA was commonly prescribed in infancy before transitioning to PPI. Growth improvements were not significantly greater, while GM  $\alpha$ -diversity at 3 years of age was significantly lower and early-onset lung disease more severe, in persistent ABT users compared to nonusers of ABT.

**Conclusion:** In our cohort of young children with CF, early and persistent ABT use was not associated with significant growth benefits and instead showed associations with reduced GM diversity and negative effects on early-onset lung disease. Consequentially, there is a critical need for systematic evaluation and comprehensive risk–benefit analysis of ABT to ensure proper guidelines for children with CF.

**Abbreviations:** ABT, acid blocker therapy; CF, cystic fibrosis; CFELD, cystic fibrosis early-onset lung disease; FIRST, Feeding Infants Right... from the STart; GERD, gastroesophageal reflux disease; GM, gut microbiome; H2RA, H2 receptor antagonist; PA, *Pseudomonas aeruginosa*; PERT, pancreatic enzyme replacement therapy; PEx, pulmonary exacerbation; PI, pancreatic insufficiency; PPI, proton pump inhibitor; PS, pancreatic sufficiency.

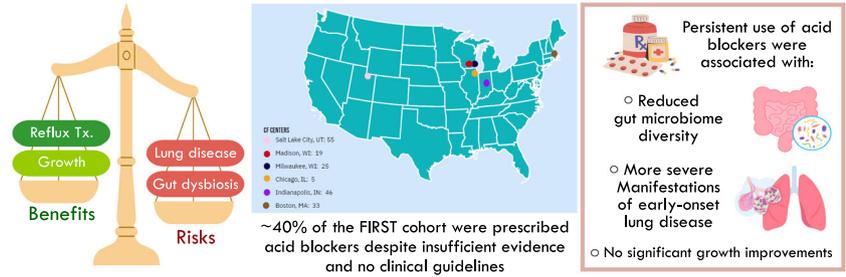
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## Impact of acid blocker therapy on growth, gut microbiome and lung disease in young children with CF

Cohort of 145 infants born 2012-17, diagnosed with cystic fibrosis (CF) through newborn screening, and evaluated in a prospective multi-center longitudinal study known as FIRST from early infancy to 36 months of age



**Conclusion:** Acid blocker therapy in our study cohort was associated with greater risks than benefits. Further research to guide prescribing practice of acid blocker therapy is needed.

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## KEYWORDS

gastroesophageal reflux, malnutrition, pancreatic insufficiency, proton pump inhibitors, pulmonary exacerbation

## 1 | INTRODUCTION

Cystic fibrosis (CF), caused by defective chloride channels from pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, leads to pancreatic insufficiency (PI) in about 85% of patients, recurrent respiratory infections, chronic obstructive lung disease, malabsorption, and potential malnutrition.<sup>1</sup> Malabsorption due to PI requiring pancreatic enzyme replacement therapy (PERT)<sup>2</sup> often begins during infancy, and maintaining optimal growth presents a significant clinical challenge.<sup>3</sup> Gastroesophageal reflux disease (GERD) is relatively common in the CF population.<sup>4,5</sup> Therefore, patients with CF who experience GERD-like symptoms are frequently prescribed acid blocker therapy (ABT) such as histamine H2 receptor antagonist (H2RA) and proton pump inhibitor (PPI).<sup>6,7</sup> The goal of improving nutrient absorption in the CF population has also led to the prescription of ABT to maximize PERT efficacy<sup>8</sup> without established guidelines or proof of efficacy.

Perceived benefits of ABT for children with CF should be weighed against potential negative impacts of GERD such as irritability, chronic vomiting, malnutrition with poor weight gain or weight loss, iron deficiency, esophagitis, delayed feeding progression and other behavioral issues.<sup>9</sup> With CF diagnoses occurring routinely through newborn screening since 2010,<sup>10</sup> use of acid blockers in very young children appears to be rising, with wide variation in the age of initiation. Therefore, the objectives of the present study are to characterize ABT usage in very young children

## What is Known

- Malabsorption and growth limitations are concerns in children with cystic fibrosis (CF).
- Acid blocker therapy (ABT) is common in CF despite limited evidence of its benefits and a lack of guidelines for such treatment.
- Proton pump inhibitors are associated with adverse pulmonary and gastrointestinal outcomes.
- There are no guidelines for using ABT in CF patients.

## What is New

- ABT in our cohort of young children with CF was not associated with growth benefits.
- ABT was associated with reduced gut microbiome diversity.
- Persistent ABT users showed greater signs and symptoms of lung disease than nonusers.
- Further research to guide prescribing practice of ABT is needed.

with CF, understand the indications for initiating ABT, and investigate the associations between ABT and growth, severity of early-onset lung disease, and gut microbiome (GM) diversity by utilizing data generated from our prospective multicenter, longitudinal study known as FIRST (Feeding Infants Right... from the STart).

## 2 | METHODS

### 2.1 | Study design and population

The complete FIRST cohort and its design and data collection are described elsewhere.<sup>11–13</sup> Briefly, 183 children born during 2012–2017 and diagnosed with CF through newborn screening at six CF Centers in the United States were enrolled. Study visits were conducted in conjunction with routine clinical care according to current clinical practice guidelines,<sup>14,15</sup> that is, monthly after diagnosis until age 6 months, bi-monthly from 6 to 12 months, and every 3 months thereafter. The FIRST project was approved by the institutional review boards at all participating institutions. Informed written consent was obtained from the parents/guardians of all participating patients.

Of the 183 children enrolled in FIRST, 172 (94%), 160 (87%), and 145 children (79%) completed follow-up to age 12, 24, and 36 months, respectively. The present study included 145 children with CF born during 2012–2017 and completed their longitudinal follow-up until the youngest subject reached age 36 months in December 2020.

### 2.2 | Assessment of ABT and pancreatic functional status

At each study visit, data on the use of acid blockers and their indications were collected in the medication section of the pulmonary interval history questionnaire<sup>12</sup> by trained research coordinators. A total of 2469 medication forms were collected in the first 3 years of life. Pancreatic function was assessed at 2, 4, 6, 8, and 12 months of age and annually thereafter by fecal elastase-1 measurement. Pancreatic sufficiency (PS) and PI were defined by fecal elastase-1  $\geq 200$  and  $< 200$   $\mu\text{g/g}$ , respectively.<sup>3,11</sup>

ABT use in individual subjects was classified into three groups: nonusers who were never prescribed ABT in the first 3 years of life ( $n = 64$ ), persistent users who started ABT in infancy (age range: 1–11 months) and continued to 3 years of age ( $n = 54$ ), and occasional users that consisted of the remainder of the subjects ( $n = 27$ ). Occasional users were a heterogeneous group and included those who started ABT later at age 14–27 months ( $n = 5$ ), who used ABT temporarily, that is, stopped ABT in the second year of life ( $n = 14$ ), and who used ABT intermittently, that is, on and off during the first 3 years of life ( $n = 8$ ).

### 2.3 | Growth assessment

As described previously,<sup>13</sup> recumbent length ( $\leq 2$  years of age), standing height ( $> 2$  years of age),

and weight were measured at each study visit. A total of 3120 growth measurements were used to calculate age- and sex-specific z-scores for weight-for-age (WAZ), length-for-age or height-for-age (LAZ/HAZ), and body mass index-for-age (BMIZ) by using the WHO references for age 0–24 months and CDC references for age 25–36 months as recommended by the CDC and the American Academy of Pediatrics.<sup>16,17</sup>

### 2.4 | Assessment of cystic fibrosis early-onset lung disease (CFELD)

The development of the CFELD scoring system was recently published.<sup>12</sup> Briefly, clinical manifestations of CF lung disease, that is, respiratory symptoms, pulmonary exacerbations (PEX), *Pseudomonas aeruginosa* (PA) infections, and hospitalizations, were recorded systematically on a pulmonary interval history form at visit (totaling 2469 visits in the first 3 years of life). These data were used to derive CFELD scores<sup>12</sup> as explained in more detail in Supporting Information S1: Supplement 1. The overall CFELD scores (ranging from zero [best] to 15 [worst]) as well as two subscores (PEX and PA infections) were used to compare lung disease severity by use of ABT.

### 2.5 | Assessment of GM diversity

GM assessment was initiated in 2017 using stored stool samples collected annually for fecal elastase-1. Among the 145 subjects included in the present study, 139 had 271 stool samples from the first 3 years of life available for GM analysis. All samples from persistent users and 87% of the samples from occasional users were collected while using ABT.

As described previously,<sup>18</sup> fecal DNA extractions were performed by using PowerSoil DNA Isolation Kit (Mo Bio, Cat # 12888) or QIAamp<sup>®</sup> 96 PowerFecal QIAcube<sup>®</sup> (Qiagen Cat #51531), followed by 16S rRNA gene sequencing at UW-Madison's Biotechnology Center using the Illumina MiSeq, with paired-end, 250 bp sequencing (allowing a total span of up to 500 bases), resulting in at least 100,000 reads per individual sample. Primary analysis and index demultiplication are achieved via Illumina bcl2fastq 1.8.2. Analysis of metagenomic data on 16S rRNA gene sequencing data was performed by the staff at the Bioinformatics Resource Core within the UW-Madison Biotechnology Center by using a commonly used method<sup>19</sup> with the QIIME pipeline (<http://qiime.org/>).<sup>20</sup> Two measurements, namely, GM richness represented by the number of genera, and the Shannon index as a measure of  $\alpha$ -diversity<sup>21</sup> were used to compare GM diversity by use of ABT.

## 2.6 | Statistical analysis

All statistical analyses comparing three ABT user groups were performed by using SAS (version 9.4). Univariate analyses included comparisons of means by the analysis of variance, medians by the median test, and proportions for categorical variables by chi-square test or Fisher's exact test (when sample size was <5 in any subgroup).

Multiple regression analyses were performed to compare growth z-scores, CFELD scores, and GM diversity measures among three ABT user groups. Analysis of covariance was performed at each age of 1, 2, and 3 years. In addition, longitudinal analyses over the first 3 years of life were performed by using a mixed-effects model with repeated measures and an autoregressive covariance. All regression models were adjusted for covariates including CF characteristics (F508del genotype, PS/PI, birth weight z-score, and use of CFTR modulators), type of milk feeding (breastmilk or formula) during the first 6 months of life as defined in detail in our recent publication<sup>13</sup> and explained in Supporting Information S1: Supplement 2, use of an extensively hydrolyzed protein or amino acid-based formula, use of supplemental gastrostomy feeding, treatment with antibiotics, study site, as well as demographic and socioenvironmental factors listed in Table 1.

## 3 | RESULTS

### 3.1 | Prevalence and types of ABT

Table 1 shows the characteristics of the study population. In our study cohort, the prevalence of ABT use during the first 3 years of life was 56% (81/145) and was significantly higher in children with PI (60%, 76/126) versus PS (26%, 5/19), in children fed fortified milk in the first 6 months of life (70%, 64/92) versus those fed unfortified milk (32%, 17/53), in children fed an extensively hydrolyzed protein or amino acid-based formula (78%, 14/18) versus those fed breastmilk or standard formula (53%, 67/127), in children who received supplemental gastrostomy feeding (86%, 18/21) versus those fed orally (51%, 63/124), and in children who were treated with antibiotics (63%, 66/105) versus those who did not (38%, 15/40). Two thirds of ABT users were persistent users and one third were occasional users; most of them were prescribed with H2RA followed by PPI (Supporting Information S1: Supplement 3). No significant differences in demographic and socioenvironmental characteristics were observed among the three ABT user groups.

### 3.2 | Indications and center variation in prescribing ABT

In our medication data, GERD was the predominant indication (recorded in 60% of the forms) for initiation of ABT. PERT, other gastrointestinal (GI) symptoms (unspecified), or a combination of GERD, PI, and PERT augmentation were also reported as indications. Ten percent of the patients treated with ABT had no documented indication for their initiation of ABT in our medication records. A large center variation in ABT use was observed, ranging from 19% to 100%.

In a separate brief survey (Supporting Information S1: Supplement 4) sent to the Pediatric CF Centers participating in the FIRST project, all reported no specific protocol with defined criteria that were followed in their center for initiating ABT in children with CF. Regarding factors or indications that led to clinical decisions for initiation, most centers responded to our survey that ABT was initiated due to concerns for GERD, PERT, or growth. PI was not reported as a factor in decision-making for ABT initiation in all centers in this survey despite PI being recorded as an indication for ABT initiation in the medication forms of 12 children with CF in our cohort.

### 3.3 | Growth outcomes

As shown in Figure 1, no significant differences were found among persistent, occasional, and nonusers of ABT in the first 3 years of life in all growth z-scores. There was also no significant difference in the percentage of children whose WAZ, LAZ/HAZ, and BMIZ improved from 3 months to 3 years of age among the three ABT user groups. On the other hand, multiple regression analyses revealed that birth weight z-score and type of milk feeding in the first 6 months of life were significant predictors of growth z-scores.

### 3.4 | CFELD outcomes

As shown in Figure 2A, overall CFELD scores in the first 3 years of life were significantly higher (worse) in persistent users of ABT compared to nonusers. Occasional users of ABT also showed higher CFELD scores, but the *p* value was not significant compared to nonusers. The PEx subscores in the first 3 years of life were significantly worse in persistent users compared to nonusers of ABT (Figure 2B). These findings were supported by additional results showing that the overall CFELD score and the PEx subscore increased (worsened) more from age 1 to 3 years (Figure 2C) in persistent users of ABT. The prevalence of ever positive PA cultures by age 3 years did not differ

**TABLE 1** Characteristics of the study population.

	Overall	ABT groups			<i>p</i> <sup>a</sup>
		Nonusers	Occasional users	Persistent users	
Number of subjects	145	64	27	54	
CF characteristics					
<i>CFTR</i> genotype					0.53
F508del/F508del	74 (51%)	33 (52%)	12 (44%)	29 (54%)	
F508del/other	59 (41%)	28 (44%)	11 (41%)	20 (37%)	
Other/other	12 (8%)	3 (5%)	4 (15%)	5 (9%)	
Pancreatic phenotype					0.010
PI	126 (87%)	50 (78%)	24 (89%)	52 (96%)	
PS	19 (13%)	14 (22%)	3 (11%)	2 (4%)	
Birth weight z-score	-0.2 ± 1.0 (-0.1) <sup>b</sup>	0.0 ± 0.9 (0.0)	-0.1 ± 1.0 (-0.1)	-0.5 ± 1.1 (-0.5)	0.017
CFTR modulator therapy before 3 years of age (ivacaftor or ivacaftor/lumacaftor)	29 (20%)	14 (22%)	7 (26%)	8 (15%)	0.43
Milk feeding in the first 6 months of life <sup>c</sup>					
Unfortified	53 (37%)	26 (56%)	8 (30%)	9 (17%)	<0.001
Fortified	92 (63%)	28 (44%)	19 (70%)	45 (83%)	
Within unfortified					0.06
Predominant breastmilk	22 (42%)	13 (36%)	2 (25%)	7 (78%)	
Partial breastmilk/partial formula	13 (25%)	8 (22%)	3 (38%)	2 (22%)	
Predominant formula	18 (34%)	15 (42%)	3 (38%)	0	
Within fortified					0.38
Predominant breastmilk	22 (24%)	5 (8%)	6 (22%)	11 (20%)	
Partial breastmilk/partial formula	39 (42%)	11 (17%)	10 (37%)	18 (33%)	
Predominant formula	31 (34%)	12 (19%)	3 (11%)	16 (30%)	
Use of extensively hydrolyzed protein or amino acid-based formula					0.041
Yes (ever)	18 (12%)	4 (6%)	7 (26%)	7 (13%)	
No (never)	127 (88%)	60 (94%)	20 (74%)	47 (87%)	
Use supplemental gastrostomy feeding					0.004
Yes (ever)	21 (15%)	3 (5%)	4 (15%)	14 (26%)	
No (never)	124 (85%)	61 (95%)	23 (85%)	40 (74%)	
Treatment with antibiotics <sup>d</sup>					<0.001
Yes (ever)	105 (72%)	39 (61%)	17 (63%)	49 (91%)	
No (never)	40 (28%)	25 (39%)	10 (37%)	5 (9%)	
Demographic and socioenvironmental characteristics					
Female sex	66 (46%)	26 (41%)	13 (48%)	27 (50%)	0.57
Race: non-White	4 (3%)	3 (5%)	0 (0%)	1 (2%)	0.53
Ethnicity: Hispanic	7 (5%)	4 (6%)	2 (7%)	1 (2%)	0.41
Parental education: community college or above					0.23

TABLE 1 (Continued)

	Overall	ABT groups			$p^a$
		Nonusers	Occasional users	Persistent users	
Both parents	91 (63%)	39 (61%)	21 (78%)	31 (57%)	
One parent	23 (16%)	8 (12%)	3 (11%)	12 (22%)	
Neither parent	31 (21%)	17 (27%)	3 (11%)	11 (20%)	
Household annual income					0.62
<\$40,000	43 (30%)	16 (25%)	7 (26%)	20 (37%)	
\$40,000–\$79,000	48 (33%)	21 (33%)	10 (37%)	17 (31%)	
≥\$80,000	54 (37%)	27 (42%)	10 (37%)	17 (31%)	
Having older sibling(s) with CF	20 (14%)	6 (10%)	7 (26%)	7 (13%)	0.11
Receiving Medicaid or other public insurance	54 (37%)	23 (36%)	6 (22%)	25 (46%)	0.10

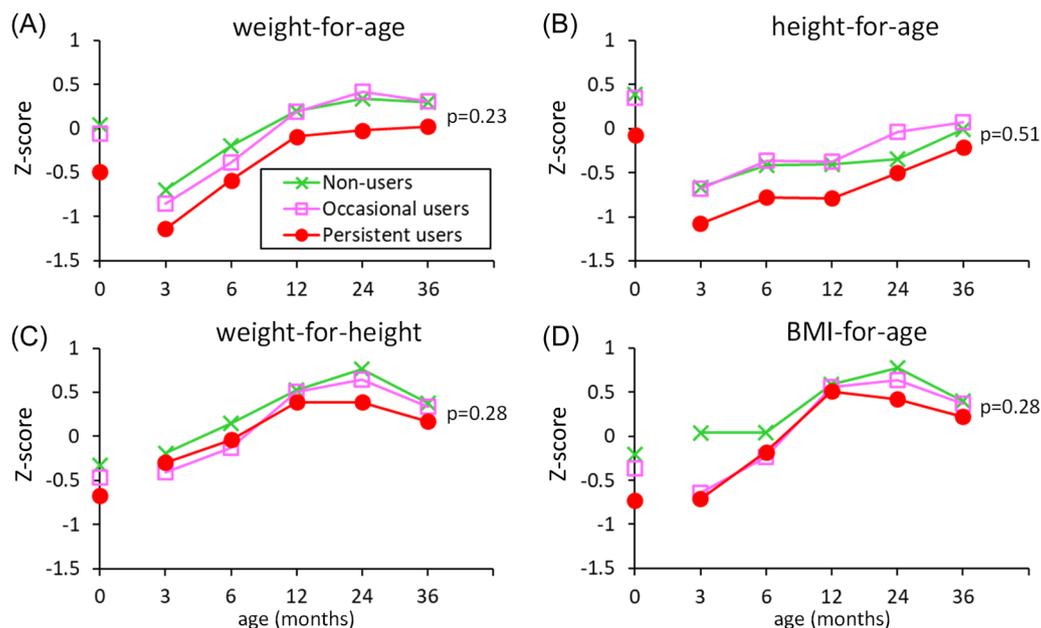
Abbreviations: ABT, acid blocker therapy; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficiency; PS, pancreatic sufficiency.

<sup>a</sup>Comparing three ABT groups.

<sup>b</sup>Values are mean  $\pm$  SD (median).

<sup>c</sup>Described in Lai et al.<sup>13</sup> and Supporting Information S1: Supplement 2.

<sup>d</sup>Prescribed by the CF care providers, that is, no antibiotics data from the primary care providers.



**FIGURE 1** Comparison of growth z-scores in the first 3 years of life by ABT groups. The definitions for persistent and occasional users are described in Section 2.  $p$  Values indicate no significant differences in growth z-scores comparing the three ABT groups as assessed by multiple regression models adjusting for potential confounders stated in Section 2. ABT, acid blocker therapy; BMI, body mass index.

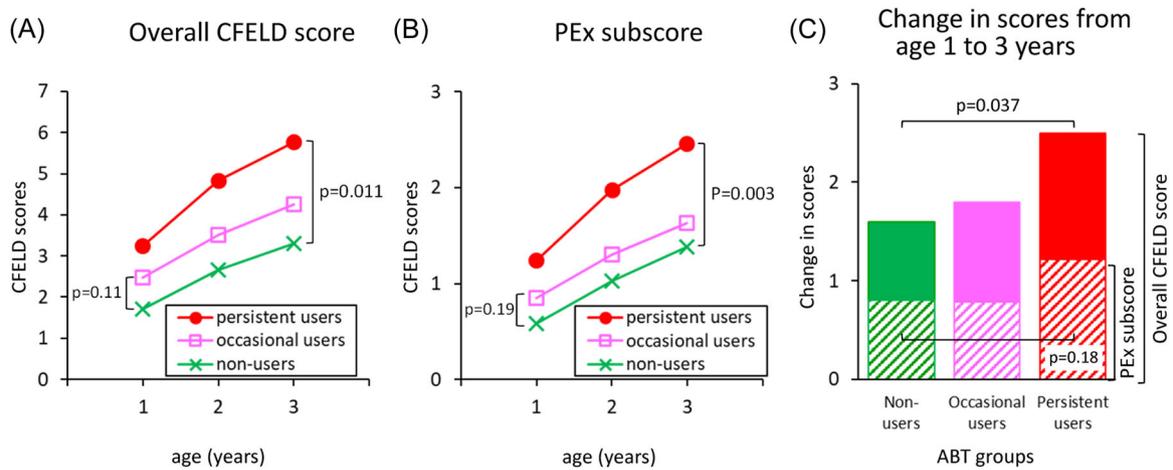
significantly among the three ABT user groups (34% in nonusers, 44% in occasional users, and 41% in persistent users;  $p = 0.88$ ).

In addition to ABT, supplemental gastrostomy feeding and treatment with antibiotics were associated with worse CFELD scores. On the other hand, children with CF who were fed fortified breastmilk in the first 6 months of life exhibited better CFELD scores than

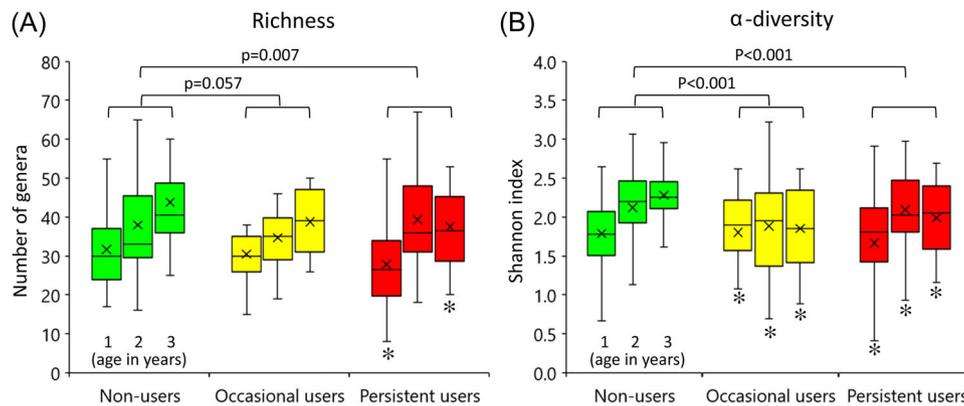
those fed fortified formula, which was consistent with our recent report.<sup>13</sup>

### 3.5 | GM outcomes

As shown in Figure 3A, the richness of fecal microbiome as reflected by the number of genera



**FIGURE 2** Comparison of CFELD in the first 3 years of life by ABT groups. The definitions for persistent and occasional users are described in Section 2. Overall CFELD scores (A), PEx subscores (B), and the change in CFELD scores from age 1 to 3 years (C) were significantly higher (worse) in persistent users compared with nonusers. *p* Values were adjusted for potential confounders, as stated in Section 2. ABT, acid blocker therapy; CFELD, cystic fibrosis early-onset lung disease; PEx, pulmonary exacerbation.



**FIGURE 3** Comparison of GM richness (A) and  $\alpha$ -diversity (B) at age 1, 2, and 3 years by ABT groups. The definitions for persistent and occasional users are described in Section 2. GM  $\alpha$ -diversity, as reflected by Shannon index (B), was significantly lower in both persistent users and occasional users when compared with nonusers. *p* Values were adjusted for potential confounders, as stated in Section 2. Asterisks indicate point-wise *p* < 0.05 compared with nonusers at each year of age. ABT, acid blocker therapy; GM, gut microbiome.

increased with age in the first 3 years of life in nonusers and occasional users of ABT, but this age trend was dampened in persistent users of ABT from age 2 to 3 years. A similar age trend was observed in the  $\alpha$ -diversity measure Shannon index in nonusers of ABT (Figure 2B), but this trend was significantly diminished in occasional users and persistent users when compared to nonusers of ABT. Point-wise *p* values supported this finding, showing that Shannon index differed significantly between ABT users and nonusers at ages 1, 2, and 3 years. In addition to ABT, the type of milk feeding in the first 6 months of life was also a significant predictor of the GM diversity. Specifically, Shannon index was significantly higher in children with CF who received predominant breastmilk regardless of fortification or not ( $2.065 \pm 0.470$ ), compared with those who received

partial breastmilk ( $1.848 \pm 0.572$ ) or predominant formula ( $1.959 \pm 0.608$ ).

## 4 | DISCUSSION

Results from our FIRST cohort of infants and toddlers with CF showed that prolonged ABT was not associated with significant improvements in growth but instead significant negative alterations to the GM and progression of early-onset lung disease. Evidence from our study is in line with the growing body of literature advocating for more judicious PPI therapy as it has been associated with adverse outcomes such as pulmonary infections, fractures, and anemia.<sup>22–24</sup> These findings reinforce the concern that acid blockers are not benign, although the mechanisms of ABT effects on

these health outcomes are not clear in our study population. The prevalence of ABT in our cohort parallels nationwide trends showing PPIs and H2RAs are used in about half of children with CF.<sup>8</sup> ABT has evolved into a commonly used modality without strong evidence to support the assumed growth benefits, while risks have not been examined systematically in CF.<sup>25</sup> We also observed large variation in prescription practices across centers in our study which substantiates the lack of consensus for ABT use in pediatric patients with CF.

Previous studies of acid blockers in CF populations reported negative pulmonary associations such as PA infections, PExs,<sup>26–30</sup> and altered respiratory microbiome.<sup>31,32</sup> To our knowledge, our study was the first to demonstrate a significantly greater risk of PExs associated with ABT in such a young CF population (infants and toddlers). Nevertheless, all of these studies were observational and indicated associations instead of causality.

With regard to our GM findings, studies have also shown higher risk for GI-related admissions during the first 12 months with PPI therapy in CF.<sup>33</sup> In non-CF populations, PPI-induced hypochlorhydria was suggested to facilitate colonization of disadvantageous microbiota.<sup>34</sup> Recent reviews in the role of gut microbiota in lung diseases<sup>35</sup> including CF<sup>36</sup> have also described the concept of an altered “gut-lung axis” in children with CF and its potential effect in modulating the immune system.

We acknowledge the colloquial practice of using ABT as adjuvant therapy to optimize PERT and thereby improve growth and nutritional needs in CF. It was unclear in our study whether PI as an indication was used as a proxy for PERT augmentation, as inadequate buffering in CF from physiologic bicarbonate is the proposed cause of poor PERT efficacy. However, very few studies regarding the use of ABT in this capacity exist, and virtually no published studies in infants and toddlers with CF exist in the literature.

For potential alternatives to managing GERD in young children with CF, we suggest those described in the current pediatric GER clinical practice guidelines<sup>37</sup> such as avoiding overfeeding, thickening feeds, considering 2–4 weeks of an extensively hydrolyzed protein or amino acid-based formula for formula-fed infants, considering the use of head elevation or left lateral positioning after infancy, as well as referral to a pediatric gastroenterologist if these alternative therapies are ineffective. Given the clinical difficulty of routinely diagnosing reflux disease with endoscopic pH monitoring in children, physiologic spit-up that peaks at 4 months and typically stops at 12 months should be well delineated from pathologic reflux. The lack of clearly defined indications to serve as the criteria for prescribing ABT from the CF centers participating in our study also underscores the need to

develop clinical practice guidelines for the CF population, thereby reducing inappropriate use of PPI—an important message stated in the 2013 report by the American Academy of Pediatrics.<sup>38</sup>

It is also worth noting that discontinuation of PPIs often leads to transient GI symptoms due to rebound acid hypersecretion. This is to say that even if PPIs are not harmful, there are further considerations for successfully tapering off these medications. Those with prolonged PPI therapy may have started early in infancy without review over time in a population that already is faced with a large medication burden. Nationwide data from the CF Foundation Patient Registry showed that the prevalence of acid blocker use in children was 62% in the early 2010s<sup>39</sup> and remained relatively prevalent at 40% in 2022.<sup>8</sup>

Our study is limited in that we only assessed ABT's associations with three outcomes, namely growth, GM, and early-onset lung disease. These were selected as they are conceived benefits or risks of ABT from the literature, though other associations with ABT exist. Another limitation is that CFELD has also not been validated in multiple CF populations yet as a metric for lung disease. Although our study in the first 3 years of life may be viewed as a limitation, it is also a strength considering the fact that the first 1000 days of life is a critical period of development and a paucity of data exists. We did not compare the effects between H2RA and PPI, which requires future investigation. Finally, our findings only apply to the CF population, as we do not have data from healthy children receiving ABT for comparison.

In conclusion, ABT in our cohort of very young children with CF was not found to be associated with growth benefits. Instead, we observed that prolonged use of ABT was associated with more severe lung disease and reduced GM diversity. The associations observed in our study warrant future research using randomized clinical trials to definitively determine the benefits and risks of ABT in children with CF. Equally important, more research is required to identify and investigate interventions that may mitigate the potential negative impact of ABT on GM diversity in infants and toddlers with CF. In the meantime, given that there are currently no evidence-based clinical guidelines for PPI use in the pediatric CF population and documented adverse impacts of chronic PPI use in pulmonary and microbiome outcomes, we recommend more cautious and selective ABT in CF as ABT is not inconsequential.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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