# Does probiotic supplementation affect pulmonary exacerbation and intestinal inflammation in cystic fibrosis: a systematic review of randomized clinical trials

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***Background:*** **Patients with cystic fibrosis (CF) usually have abnormal intestinal microbiota due to massive exposure to antibiotics. Probiotics could modify the gut microbiota and hence may affect CF management. So the aim of present systematic review was evaluation of the efficacy and safety of probiotic supplementation for the management of cystic fibrosis.**

***Data sources:*** **We searched PubMed, Science Direct, Google Scholar, Springer Cochrane Library Databases until January 2016 for randomized controlled trials (RCTs) performed in pediatric or adult populations related to the study aim. Key words were selected based on Mesh terms. Based on the Critical Appraisal Skills Programme checklist, eligibility of included articles was evaluated.**

***Results:*** **Five studies included in this review represent 188 participants with a follow up period ranging from 1 month to 6 months. The results of the included studies supporting the use of probiotics in management of pulmonary exacerbation and intestinal calprotectin in patients with cystic fibrosis. However the level of evidence was limited.**

***Conclusion:*** **The lack of high quality RCTs makes it impossible to support a general recommendation about the use of probiotics in the treatment of CF pulmonary exacerbation and intestinal inflammation.**

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***Key words:*** **cystic fibrosis;**
**intestinal inflammation;**
**probiotics;**
**pulmonary exacerbation**

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Review article

## Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited disease caused by mutations in the CF transmembrane regulator (*CFTR*) gene.[1] CTFR is a cyclic adenosine monophosphate-regulated chloride channel that also regulates the flow of bicarbonate and other ions across the apical surface of epithelial cells. The mutation of this gene results in the formation of viscous mucus and consequently affects multiple organs, including the lungs and digestive tract.[2,3]

In CF patients, abnormal intestinal mucosa may be associated with distorted gut microbiota. These patients usually have abnormal intestinal microbiota as a result of massive exposure to antibiotics.[4-7] The altered microbiota is involved in regulatory and pro-inflammatory immune pathways, which may cause systemic inflammation in CF patients.[8]

So far, only a limited number of studies have examined gut microbiota in CF. Observational studies have shown the suppression of phyla Firmicutes and Bacteroidetes in CF patients and an increase in pathogenic Enterobacteriaceae and *Fusobacterium* spp.[9,10] The presence of the *Fusobacterium* spp. provides a reservoir for airway infiltration via fecal-oral transmission.[11] Elevated levels of *Fusobacterium* and *Bacteroides* may adhere to the intestinal epithelium and predispose the CF gut to infection and inflammation.[12]

Diet can influence gut microbiota composition to optimize the microbial interaction with the intestinal mucosa and consequential immune responses and nutrient metabolism in CF. One of the dietary strategies that can modify the gut microbiota and hence affect CF management is probiotic supplementation.

Probiotics are defined as "live microorganisms, which when administered in adequate amounts confer a health

benefit on the host".[6] Emerging evidence from human and animal model studies indicate promising outcomes for the use of probiotics in improving conditions associated with inflammation, such as cardiovascular disease and inflammatory bowel disease.[13,14] Furthermore, some clinical trials studied the effect of probiotic and symbiotic supplementation on pulmonary exacerbation, gut complication, and quality of life in CF patients.[15-20] Despite a narrative review study on the use of probiotics in CF, there is no systematic review on the effect of probiotic supplementation on lung exacerbation and intestinal complications in such patients. The aim of the present study was to evaluate the effects of probiotic supplementation on pulmonary exacerbation and intestinal complications in CF.

## Methods

### Inclusion criteria of studies in this systematic review

We included studies which met the following criteria: 1) types of studies: randomized controlled trials (RCTs) of any duration that compared any type of probiotic with placebo, irrespective of their language or publication status were included in this study; 2) types of participants: we included studies that assessed the use of probiotics in any age group. 3) types of interventions: studies that used any probiotic supplementation, irrespective of formulation, microorganism, supplement composition (single *vs*. multiple strains) or dose, were included; 4) types of outcome measures: the following outcomes were believed critical to the decision regarding whether to use probiotics to manage CF; 5) with primary outcome: pulmonary exacerbation, increase in pulmonary symptoms and airway secretions, as reported by the CF Foundation Criteria; 6) with secondary outcome: intestinal inflammation, indicated by fecal calprotectin quantification.

We searched the databases of PubMed, Science Direct, Google Scholar, Springer and the Cochrane Library for articles published up until January 2016. Key words were selected based on Mesh terms and included (but not limited to): "probiotic" or "*Lactobacillus* GG", "*Lactobacillus reuteri*", "cystic fibrosis", "intestinal inflammation", "calprotectin" and "pulmonary exacerbation". The references of recent reviews and other eligible articles were manually searched for additional trials not identified by the electronic search. We also searched clinicaltrials.gov for ongoing studies. Two reviewers extracted data independently. An initial screening of search results was done by one reviewer to exclude duplication data and irrelevant records. Two reviewers independently screened the remaining records to identify which potentially relevant records met the inclusion/exclusion criteria. Full papers were obtained for these records and were independently assessed for relevance by two reviewers. Any discrepancies were resolved through discussion and by consulting a third reviewer. For each eligible trial, data on the study method, population characteristics, and results

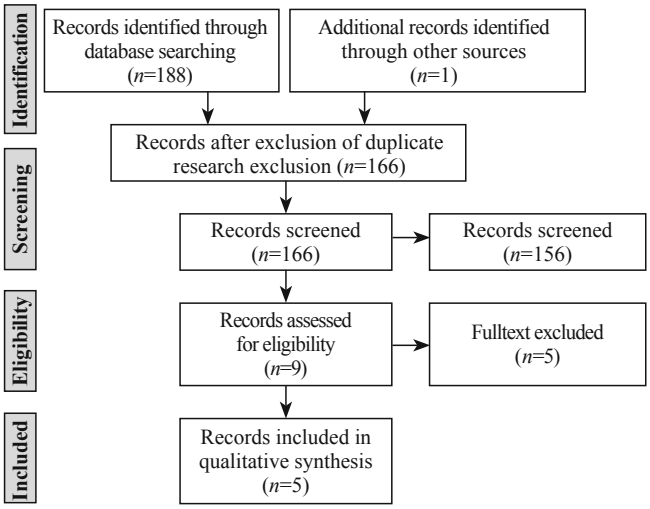


**Fig.** Flow diagram of trials for inclusion in the systematic review.

**Table 1.** Characteristics of included randomized clinical trials

| Author, year | Type of study | Sample size | Age (y) | Intervention | Placebo | Dosage (CFU/d) | Duration (mon) | Allocation concealment/ blinding/ITT analysis/ comprehensive follow up |
|---|---|---|---|---|---|---|---|---|
| Bruzzes et al, 2014[17] | Parallel RCT | 22 | 2-9 | *Lactobacillus rhamnosus* GG | Maltodextrine/ magnesium stearate | $6\times10^9$ | 1 | Yes/Yes/Yes/Yes |
| del Campo et al, 2014[21] | Parallel RCT | 30 | 8-44 | *Lactobacillus reuteri* | ND | $10^8$ | 6 | Yes/Yes/No/Yes |
| Di Nardo et al, 2014[22] | Parallel RCT | 61 | 6-29 | *Lactobacillus reuteri* | ND | $10^{10}$ | 6 | Yes/Yes/No/Yes |
| Jafari et al, 2013[23] | Parallel RCT | 37 | 2-12 | *Lactobacillus casei*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. infantis* | All ingredient of probiotic capsule except active ones | $2\times10^9$ | 1 | No/Unclear/Yes/Yes |
| Bruzzes et al, 2007[19] | Cross-over RCT | 38 | 5-23 | *Lactobacillus rhamnosus* GG | ORS | $6\times10^9$ | 6 | Unclear/Yes/No/Yes |

Probiotic versus no probiotic in cystic fibrosis for management of pulmonary exacerbation and intestinal inflammation. RCT: randomized controlled trial; ORS: oral rehydration salts; CFU: colony-forming units; ND: not determined; ITT: intention to treat.

were extracted by one reviewer and checked by a second reviewer.

### Quality assessment

Two investigators independently rated the methodological quality of selected studies using the Critical Appraisal Skills Program (Public Health Resource Unit, Oxford, UK) checklist for RCTs. After critical appraisal of articles, five RCT articles were selected (Fig.). The characteristics of these five studies are presented in Table 1.

### Statistical methods

As the included studies were not sufficiently similar or of sufficient quality, the meta-analysis of the included studies could not be performed. The binary measure for individual studies is reported as the odds ratio (OR) between the experimental and control groups, with 95% confidence intervals (CI). The mean difference (MD) between the treatment and control groups was selected to represent the difference in continuous outcomes (with 95% CI).

## Results

Through the systematic search, nine trials[15-23] which assessed the effect of probiotic supplementation in CF patients, were identified. One study assessed neither pulmonary exacerbation nor intestinal inflammation,[15] one used symbiotic sachet (probiotic+fructooligosaccharide)[16] and two were not randomized placebo-controlled clinical trial; therefore, they were not included in the present systematic review.[18,20] Thus, five articles[17,19,21-23] consisting of a total of 188 subjects, met the predefined inclusion criteria. The characteristics of the included studies are presented in Table 1.

All the trials were full peer-reviewed publications. Four of the included studies were parallel design RCTs,[17,21-23] and one had a crossover design.[19] The participant's age was in the range 2-44 years. Four of the five trials reported the source of trial funding;[17,19,22,23] of these, none received funding from the industry.

The methodological quality of the trials varied. The randomization method was described and adequate in only two RCTs.[19,22] Double blinding was applied in all RCTs. The withdrawals and dropouts were adequately described in all the studies, and all of the studies included an adequate number (i.e., ≥80%) of participants in the final analysis.

### Participants

The five studies included in this review comprise a total of 188 participants. Sample sizes ranged from 22 to 61. Only two studies described the detail of sample size calculations and the final sample size in one study was less than the calculated sample size. The age of participants was consistent across studies. Three studies reported sweat chloride tests as the CF diagnostic test. Two trials did not mention any diagnostic method to confirm CF.

### Interventions

One study evaluated a combination of bacteria (*Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus bulgaricus, Streptococcus thermophilus, Bifidobacterium breve, and Bifidobacterium infantis*) compared to placebo over a 1-month period;[23] two trials examined *Lactobacillus* GG[17,19] and two studies examined *Lactobacillus reuteri*.[21,22] The following different probiotic strains were tested: *Lactobacillus casei*, *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium bifidum, Lactobacillus acidophilus, Bifidobacterium infantis,* and *Lactobacillus bulgaricus*. The composition of placebo was not reported in two studies.

The duration of the interventions in the parallel-design studies were 1[17,23] and 6 months,[21,22] and 6 months in the crossover design study.[19] The doses of the probiotic supplements ranged from $10^8$ to $10^{10}$ colony-forming units (CFU)/day.

### Outcomes

del Campo et al[21] studied the effect of 6-month supplementation of $10^8$ CFU/day *Lactobacillus reuteri* in 30 CF patients for 6 month. Primary outcomes measured were fecal calprotectin and fecal inflammatory parameters. The secondary outcomes measured were body weight, body mass index (BMI) and percentage of forced expiratory volume in 1 second (%$FEV_1$). There were no significant differences between the probiotic and placebo groups in the terms of weight ($P$=0.95), BMI ($P$=0.98) and %$FEV_1$ ($P$=0.003). However, the level of fecal calprotectin was significantly lower in the probiotic group compared with the placebo group ($P$=0.03). The improvement of gastrointestinal comfort was significantly higher in the probiotic group compared with the placebo group [probiotic *vs*. placebo: 33.8±23.5 *vs*. 20.3±19.3, MD=13.5 (95% CI: -4.47 to 31.47), $P$=0.003] (Table 2). There were no significant differences between groups in terms of fecal concentration of inflammatory factors including interleukine (IL)-8, IL-1B, IL-6 and tumor necrosis factor (TNF)-alpha.

Bruzzese et al[17] investigated the effect of *Lactobacillus* GG ($6\times10^9$) supplementation for 1 month in CF children in comparison with placebo (the same composition as a probiotic, except for the active ingredient). The primary outcome measured was fecal calprotectin. There was a significant reduction in

**Table 2.** The summary of study outcomes

| Author, year | Probiotic | Results |
|---|---|---|
| Bruzzes et al, 2014[17] | *Lactobacillus rhamnosus* GG | **Fecal calprotectin (primary outcome):** Probiotic group: 0 *vs*. 4 wk, 164±70 *vs*. 78±54 μg/g, MD=86.7 (95% CI: 28.19 to 145.2), *P*<0.05 Placebo: 0 *vs*. 4 wk, 251±174 *vs*. 176±125 μg/g, MD=75 (95% CI: -51.60 to 201.61), *P*=0.3 Probiotic *vs*. placebo group: MD=28.4 (95% CI: -27.94 to 84.74) |
| del Campo et al, 2014[21] | *Lactobacillus reuteri* | **Fecal calprotectin (primary outcome):** Intervention *vs*. placebo: 33.8±23.5 *vs*. 20.3±19.3, MD=13.5 (95% CI: -4.47 to 31.47), *P*=0.003 |
| Di Nardo et al, 2014[22] | *Lactobacillus reuteri* | **Rate of pulmonary exacerbation (primary outcome):** Probiotic *vs*. placebo: 1/30 *vs*. 11/30, OR=0.06 (95% CI: 0 to 0.4), *P*<0.01 **Fecal calprotectin (secondary outcome):** Probiotic *vs*. placebo: 60.61±79.4 *vs*. -37.21±132.9, MD=-23.4 (95% CI: -80.98 to 34.18), *P*>0.05 |
| Jafari et al, 2013[23] | *Lactobacillus casei*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. infantis* | **Rate of pulmonary exacerbation (primary outcome):** Probiotic *vs*. placebo group: *P*=0.002 |
| Bruzzes et al, 2007[19] | *Lactobacillus rhamnosus* GG | **Rate of pulmonary exacerbation (primary outcome):** Probiotic *vs*. oral rehydration salts group: *P*=0.003 |

MD: mean difference; CI: confidence intervals; OR: odds ratio.



fecal calprotectin after 1 month of supplementation in the probiotic group compared with baseline [164±70 *vs*. 78±54 μg/g, MD=86.7 (95% CI: 28.19 to 145.2), *P*<0.05]. However, in the placebo group, the reduction in fecal calprotectin was not significant at the end of the study compared with the baseline value [251±174 *vs*. 176±125 μg/g, MD=75 (95% CI: -51.60 to 201.61), *P*=0.30]. However, there was no statistically significant difference in the term of fecal calprotectin between the two groups [probiotic *vs*. placebo group, MD=28.4 (95% CI: -27.94 to 84.74)] (Table 2).

Di Nardo et al[22] studied the effect of 6-month supplementation of $10^{10}$ *Lactobacillus reuteri* in CF patients. The primary outcome measured was pulmonary exacerbation. They showed that the risk of pulmonary exacerbations was significantly reduced in the *Lactobacillus reuteri* group compared with the placebo group [*P*<0.01, OR=0.06 (95% CI: 0-0.40)]. However, there was no statistically significant difference in the term of fecal calprotectin between the two groups [probiotic *vs*. placebo: 60.61±79.4 *vs*. -37.21±132.9, MD=-23.4 (95% CI: -80.98 to 34.18), *P*>0.05] (Table 2). Moreover, there were no significant differences between the two groups in the terms of plasmatic and also sputum concentration of TNF-alpha and IL-8.

In a parallel RCT, Di Nardo et al[22] studied the effect of mixture of bacteria supplementation with the dose of $2\times10^9$ for 1 month in 37 CF patients. The primary outcome measured was the rate of pulmonary exacerbation. The results indicated that during probiotic supplementation, none of the patients experienced pulmonary exacerbation, requiring either intravenous or oral antibiotic treatments. The number of pulmonary exacerbations was significantly reduced during the 3 months pre- to post-intervention in the intervention group (*P*=0.002) (Table 2).

In a crossover RCT, Bruzzese et al[19] reported the effect of a 6-month *Lactobacillus* GG supplementation in CF patients. The primary outcome measured was the rate of pulmonary exacerbation. They showed that the incidence of pulmonary exacerbations was significantly higher in children on placebo [oral rehydration salts (ORS)] than in those on *Lactobacillus* GG administration. Data from parallel groups showed a significantly decreased rate of pulmonary exacerbations in children receiving *Lactobacillus* GG, compared to those receiving placebo (ORS) in both periods (median: 2 *vs*. 1, range: 4 *vs*. 4, MD: 1, 95% CI: 0.1-2, *P*=0.02) (Table 2). Moreover, $\%FEV_1$ was significantly lower in the *Lactobacillus* GG group compared with the ORS group (*P*=0.02).

### Adverse events

Adverse events were not adequately reported. Of the four included studies, only one[21] reported adverse effects and stated that no adverse events were associated with this supplementation in CF patients.

## Discussion

The current systematic review aimed to investigate the effects of probiotic on pulmonary exacerbation rate and intestinal inflammation in CF patients. The main finding of the review is that there is limited evidence on this topic. Only five RCTs were identified, which comprised 188 CF patients, evaluated at follow-up periods of 1 and 6 months. The results of the included studies do support the use of probiotics in patients with CF. However, evidence is limited and conclusions should

be interpreted with caution. Of the five RCTs, only one study[17] compared within-group analysis and did not compare between-group analysis (intervention *vs*. placebo). Only one study[22] presented the results in the form of an OR. Three of the five included RCTs[19,22,23] evaluating the effect of probiotic supplementation on pulmonary exacerbation; all demonstrated positive effects of probiotic supplementation (irrespective of type of bacteria, dose, and duration of supplementation) on pulmonary exacerbation in CF patients. In addition, three of five RCTs[17,21,22] investigated the effect of probiotic supplementation on fecal calprotectin and all except one[21] failed to show the positive effect of this supplementation on reduction of fecal calprotectine. The 6-month supplementation of $10^8$ CFU/day *Lactobacillus reuteriin* 8- to 44-year old participants had a significant effect on fecal calprotectin reduction. However, Di Nardo et al[22] failed to demonstrate a significant effect of $10^{10}$ CFU/day *Lactobacillus reuteri* on reducing fecal calprotectin in 6- to 20-year old participants. del Campo et al[21] only compared the post-intervention values of fecal calprotectin between the two groups. However, Di Nardo et al[22] compared pre- and post-intervention values. Moreover, although Bruzzese et al[17] showed the significant reduction in fecal calprotectin in the intervention group, the between group difference was not statistically significant. It appears that the differences between the results of these two studies may be due to differences in statistical analytic methods and also to differences in sample size.

**Previous reports**

Previously, one review study attempted to determine the clinical significance of gut microbiota in CF and the potential for diet therapies.[24] This review, published in 2014, identified only one RCT,[19] which was included in our systematic review. It was concluded that the efficacy of different probiotic strains in CF lung disease treatment remains to be confirmed in larger trials. Our updated results include results from more RCTs. Thus, research needs to more precisely define the effects of using probiotics on reducing pulmonary exacerbation. In another systematic review published in 2016, Ananthan et al[25] attempted to evaluate the effect of probiotic supplementation on gut microbiota and pulmonary exacerbation in CF children and reported the positive effect of probiotic supplementation on pulmonary exacerbation and fecal calprotectin in CF children.[25] This systematic review included all observational and clinical trials and concluded that the quality level of studies were limited so it is impossible to support a general recommendation about the use of probiotics in the treatment of CF. In the mentioned systematic review, both RCTs and non-RCTs were included and also the conclusion was based on the before and after supplementations analysis. However, clinical practice guidelines should only be based on the recommendations of high-grade research. In this regard, we only included randomized clinical trials and also for conclusion, we considered only the results of between group differences.

Evidence from non-RCTs suggests that some probiotics are effective in reducing pulmonary exacerbation and intestinal inflammation. For instance, Weiss et al[20], in a pre-post pilot study, evaluated the effect of 6-month supplementation of two probiotic capsules, each containing the mixture of $6\times10^9$ CFU/day bacteria in ten CF patients. The results showed that, during probiotic treatment, none of the patients experienced pulmonary exacerbations, and that the exacerbation rate was significantly reduced in comparison to the previous 2 years ($P<0.002$).

In another pre-post study, Bruzzese et al[18] showed that *Lactobacillus* GG supplementation ($5\times10^9$ CFU/day for 4 weeks) significantly reduced average fecal calprotectin concentration after probiotic treatment in comparison with baseline values ($P<0.01$). However, according to Grading of Recommendations Assessment, Development and Evaluation criteria, the levels of quality of these evidences are low.

**Mechanisms of action**

Potential mechanisms whereby probiotics positively affect pulmonary exacerbation and intestinal inflammation are discussed below.

***Pulmonary exacerbation***

Preliminary data have shown that probiotics could exert an anti-infectious influence on sites other than the intestine. Animal studies have shown that *Lactobacillus* GG administration reduced *Pseudomonas* bacteremia in irradiated mice and that *Lactobacillus casei* increased the lung clearance of *Pseudomonas* in mice.[26] In addition, *Lactobacillus plantarum* inhibited the pathogenic activity of *Pseudomonas*.[27] The mechanisms whereby probiotics are proposed to affect pulmonary exacerbation are as follows: 1) modification of the intestinal microflora; 2) acceleration of the recovery of innate immune responses; 3) improvement of the specific immune mechanisms against respiratory infections; and 4) down-regulation of the pro-inflammatory pathways that can modulate aberrant inflammatory responses in the CF airway.[19,28]

In murine models, Tsay et al[29] have shown that the presence of commensal gut microbiota may help clear airway *Escherichia colicolonization* through activation of a toll-like receptor (TLR) 4 by lipopolysaccharide, a key component of the gram-negative bacterial membrane and potent mitogen. The activation of TLR4 then signals the

activation of nuclear factor kappa B, which regulates an array of molecules involved in activating innate immune responses to pathogens, including *Escherichia coli*[29] and *Pseudomonas aeruginosa*.[30]

### *Gut inflammation*

Probiotic administration improves gut symptoms in CF patients by changing gut microbiota composition. Probiotics may have anti-inflammatory effects through targeting "pattern recognition receptors" in the CF intestine. Some bacterial membranes can affect these receptors in the intestinal epithelium and consequently induce immuno-modulatory proteins. These proteins may affect the transcription of genes encoded for cytokine production and, as a result, promote the anti-inflammatory pathways.[28]

Moreover, probiotics enhance the ability of the gut barrier by inducing synthesis and assembly of tight junction proteins. Thus, probiotics may help reduce gut inflammation and related gut symptoms in individuals with CF.

Included studies in CF children reported no adverse effects associated with probiotic supplementation. A review article studies the risk of using probiotics in clinical practices and reported that probiotics are safe for use in otherwise healthy persons, but should be used with caution in some persons because of the risk of sepsis. Major risk factors for probiotic sepsis are including patients with underlying immune compromise and premature infants. Minor risk factors are including presence of central venous catheter and impaired intestinal epithelial barrier, e.g., diarrheal illness, intestinal inflammation. The author concluded that the presence of a single major risk factor or more than one minor risk factor merits caution in using probiotics.[31]

### Strengths and limitations

The advantage of our systematic review is the low risk of subjective data selection. Study searches, assessment, and data synthesis were based on predefined criteria and were performed using well-established tools by two independent reviewers. Nevertheless, our analysis has some limitations. First, publication bias cannot be excluded, i.e., negative findings are less likely to be published. Second, any systematic review is only as good as the included studies. Only some of the RCTs included in our systematic review seemed methodologically sound. Potential limitations included small sample size, unclear or inadequate allocation concealment, and no intention-to-treat analysis, inadequate information about placebo and not reporting adverse effects of supplementation, as well as using inappropriate statistical analytic techniques.

## Conclusions

This systematic review demonstrates that the lack of high quality RCTs makes it impossible to support a general recommendation about the use of probiotics in the treatment of CF pulmonary exacerbation and intestinal inflammation. This clinical uncertainty explains the need for large-scale RCTs in this regard. Until such data are available, we believe that the use of probiotics in CF should be considered investigative.

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