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TANAFFOS

Effects of Probiotics on Clinical Manifestations of Bronchiectasis: A Randomized, Triple Blinded, Placebo-Controlled Clinical Trial

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Background: Bronchiectasis is a condition characterized by abnormal and permanent bronchial constriction that leads to sputum production and bronchial infection. The current study was done to evaluate the effects of symbiotic probiotics on the clinical manifestations and exacerbation of bronchiectasis.

Materials and Methods: 26 patients in the placebo group (A) and 24 patients in the probiotic group (B) were allocated. In group A, patients took the placebo capsules two times daily for six months. In group B, patients took the LactoCare two times daily for six months.

Results: The mean age of patients was 55.73±13.62 (group A) and 54.5±12.59 years (group B). Most of the patients had consumed azithromycin in both groups. The current study demonstrated there was no statistically significant difference between the decreased rate of pulmonary exacerbations in both groups. However, a decreasing trend was shown in the rate of pulmonary exacerbations without hospitalization (P=0.610**)**. Also, there was a decreasing trend in the rate of pulmonary exacerbations leading to hospitalization (P=0.956). The most frequent etiologic pathogen was *Pseudomonas sp*. FEV1 and FVC/FEV1 ratios were higher in group B than in group A. However, there was no statistically significant difference between groups A and B (P=0.908 vs 0.403).

Conclusion: The symbiotic probiotics were not effective in the clinical improvement of bronchiectasis, consumption of antibiotics, the rate of pulmonary exacerbations with or without hospitalization, FEV1 and FEV1/FVC, and microbiological pattern.

Keywords: Bronchiectasis; Probiotics; Respiratory tract infection

INTRODUCTION

Bronchiectasis is a chronic respiratory disease with clinical symptoms of cough, sputum production, and bronchial infection with abnormal contraction and permanent bronchial dilatation (1, 2). The most common symptoms of bronchiectasis are cough, sputum production, rhinosinusitis, fatigue, hemoptysis, and chest pain (3). Treatment of bronchiectasis includes the prevention of exacerbation, reduction of symptoms, quality of life improvement, and prevention of disease progression (4, 5). In many developing countries, the exacerbation of bronchiectasis is a determining factor in healthcare costs (6). Furthermore, exacerbation of bronchiectasis is generally related to decreased quality of life, decreased lung function, and even mortality. Hence, it seems that the

therapeutic interventions should be needed to reduce the exacerbation of bronchiectasis (7, 8).

The infection control and prevention are bases of bronchiectasis treatment and include antibiotic therapy, proper bronchial drainage, immunodeficiency depletion, use of bronchodilators, and removal of bronchial obstruction in the case of any foreign body or tumor (9-12). In most severe cases of bronchiectasis, recurrent infections and repeated antibiotic use lead to antibiotic resistance (13). Recurrent infections can damage the superficial mucosal vessels and cause bleeding and, in severe cases, dangerous hemoptysis (14). Therefore, the use of new methods is very important for the prevention or treatment of this disease without using antibiotics.

Probiotics are specific living organisms in humans or animals that cause beneficial effects on the host's health by affecting the body's microbial flora (15, 16). Probiotics affect the immune system at several levels including an increase in cytokines and immunoglobulins, an increase in mononucleosis cell proliferation, activation of macrophages, increase in activities of natural killer cells, regulation of autoimmunity, and stimulation of immunity against pathogenic bacteria and protozoa (17, 18). Results of numerous studies have indicated that the use of probiotics for the prevention of upper respiratory infections has not been beneficial enough, but it has often reduced the duration and severity of disease in patients without any side effect (19, 20).

Generally, there have been few studies on the use of probiotics in pulmonary diseases. However, the successful use of probiotics in animal models has increased the possibility of using these products in pulmonary diseases in humans by stimulating the humoral and cellular immune systems (21). The current study was conducted to evaluate the effect of probiotics on clinical manifestations and exacerbation of bronchiectasis.

MATERIALS AND METHODS

In this randomized, triple -blinded, placebo-controlled clinical trial (RCT) study, patients with symptoms of bronchiectasis were eligible to be enrolled. They had been referred to the Respiratory Clinic of Razi Hospital (RCRH), between August and December 2017.

In the first step, Computerized Axial Tomography (CAT scan/CT scan) as the current gold standard method, and standard clinical diagnostic methods including lung function tests and a sputum culture or a chest X-ray of patients were conducted by a pulmonologist.

In the current study, eligible patients were allocated into placebo group (A), and probiotic group (B) by randomized block design. Eligible patients in groups A and B were treated with the same antibiotics and anti-inflammatory drugs. In the placebo group (A), patients took the placebo capsules containing flour (Zist Takhmir. Co) two times daily for six months. In the probiotic group (B), patients took the LactoCare ® (Zist Takhmir. Co) two times daily for six months. LactoCare ® is a symbiotic (probiotic + prebiotic) formulation and contains beneficial bacterial strains plus Fructooligosaccharides (FOS) as prebiotic.

In this study, patients were excluded with less than18 years old, cardiovascular disease, diabetes, pregnancy, history of transplantation, tumor, patients who were unable to complete the spirometry tests, and patients who consume Immunosuppressant drug. The informed consent forms were filled out by all patients. This study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1395.360). Registration number (IRCT code) of trial registry was IRCT2017041514085N4.

Study design

In this study, 75 patients with symptoms of bronchiectasis were identified by a pulmonologist. Since no study was found about the role of probiotics in controlling the clinical manifestations and rate of pulmonary exacerbations in patients with bronchiectasis,

the current study was designed as a pilot randomized, triple -blinded, placebo-controlled clinical trial. Therefore, 30 patients with bronchiectasis in each group were selected applying randomized block design. After obtaining informed consent from patients, eligible patients with symptoms of bronchiectasis were allocated into placebo (A) and intervention (B) groups. LactoCare ® is a symbiotic (probiotic + prebiotic) formulation and contains beneficial bacterial strains (*Lactobacillus rhamnosus*, *Lactobacillus heloticus*, *Lactobacillus casei*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Bifidobacterium Bruhe*, *Lactobacillus bulgaricus*, *Bifidobacterium longum*, *Lactobacillus plantarum*, *Bifidobacterium bifidum*, *Lactobacillus geseri*, *Streptococcus thermophilus*) plus Fructooligosaccharides (FOS) as prebiotic. This study was designed as a randomized triple-blind clinical trial. The variables of the study were assessed before intervention including age, weight, height, underlying diseases, smoking, duration of bronchiectasis, consumption of drugs, radiological findings and high-resolution CT (HRCT), spirometry, sputum culture, and history of the severity of bronchiectasis.

Data collection

Patients were monitored monthly; clinical symptoms and possible exacerbations of the disease were recorded. After 6 months, the same questionnaire was used and finally, the outcomes were compared and analyzed. Changes in symptoms, clinical manifestations, and exacerbations of the disease in each person with 6 months of the same period last year were compared using a questionnaire.

Statistical analysis

Mean values and standard deviations were calculated for each variable. Independent samples t-test was performed to compare quantitative variables with a normal distribution. Moreover, Mann–Whitney U test was used to compare the nonparametric quantitative variables. Furthermore, chi-square or fisher's exact test were used to compare qualitative variables. The comparison of variables after the intervention compared to the control group was performed using the Wilcoxon test. The SPSS software version 12.0; IBM Corp., Armonk, NY was used for the analysis of data. In this study, the statistical significance was determined as $P < 0.05$, and the statistically highly significant was determined as $P < 0.001$ (less than one in a thousand chance of being wrong).

RESULTS

In this study, 75 patients with symptoms of bronchiectasis were assessed by a pulmonologist. Out of 75 patients, 15 patients were excluded from the study not meeting the inclusion criteria, and only 60 patients were eligible to enroll. During follow-up, 10 patients were lost to follow up due to failure to self-following, failure of recovery, exacerbation of symptoms, and death. Finally, 50 patients (26 patients in the placebo group (A), and 24 patients in the probiotic group (B)) completed the study (Figure 1).

Based on the results, 12 men (46.2%) and 14 women (53.8%) were allocated in the placebo group (A), and seven men (29.2%) and 17 women (70.8%) were allocated in the probiotic group (B). The mean age of patients in the placebo group (A) was 55.73±13.62 years and in the probiotic group (B) was 54.5±12.59 years. In this study, 62% of patients were female, and there was no statistically significant difference between the two groups in terms of gender ($p = 0.216$) (Table 1). Regarding the history of bronchiectasis, 91.7% of patients had a history of bronchiectasis in symbiotic probiotics group. No statistically significant difference in history of bronchiectasis was observed between symbiotic probiotics and placebo groups ($P = 0.225$) (Table 1).

At the beginning of the study, 36%, 22%, and 28% of patients had been consumed azithromycin ($P=0.832$), ciprofloxacin ($P=0.063$), and levofloxacin (Tavanex 500mg) ($P=0.650$), respectively. At the end of the study, 20%, 18%, and 20% of patients consumed azithromycin ($P =0.077$),

ciprofloxacin (P=0.721), and levofloxacin (Tavanex 500mg) (P =0.077), respectively in symbiotic probiotics group B.

Current study demonstrated that there is no difference between symbiotic probiotics and placebo for the rate of pulmonary exacerbations, at the baseline and the end of six month (Table 2). However, results revealed a decreasing trend in the rate of pulmonary exacerbations with hospitalization (P=0.831) or without hospitalization (P=0.629) among patients who consumed symbiotic probiotics.

There was no statistically significant difference between the placebo group (A), and in the probiotic group (B) in terms of sputum culture of patients with bronchiectasis at the beginning of the study (P=0.412), and at the end of the study (P=0.999) (Table 3). The most frequent etiologic pathogens which isolated from the sputum samples of patients with bronchiectasis were *Pseudomonas sp.* at the beginning of the study (68.8%) and the end of the study (50%), in both groups. Other bacteria with lower prevalence including *Acinetobacter sp.*, *Citrobacter sp.*, *Candida sp.*, *Enterobacter sp.* and *Klebsiella pneumoniae* were also isolated from patients with bronchiectasis (Table 3).

In addition, qualitative analysis of HRCT finding showed that the various lung involvements in patients with bronchiectasis were not statistically significant between the placebo group (A), and probiotic group (B) at the end of the study (Table 4).

Based on the results, FEV1 and FVC/FEV1 ratios were higher in the probiotic group (B) than the placebo group (A); however, these differences were not statistically significant (P=0.908 and 0.403, respectively).

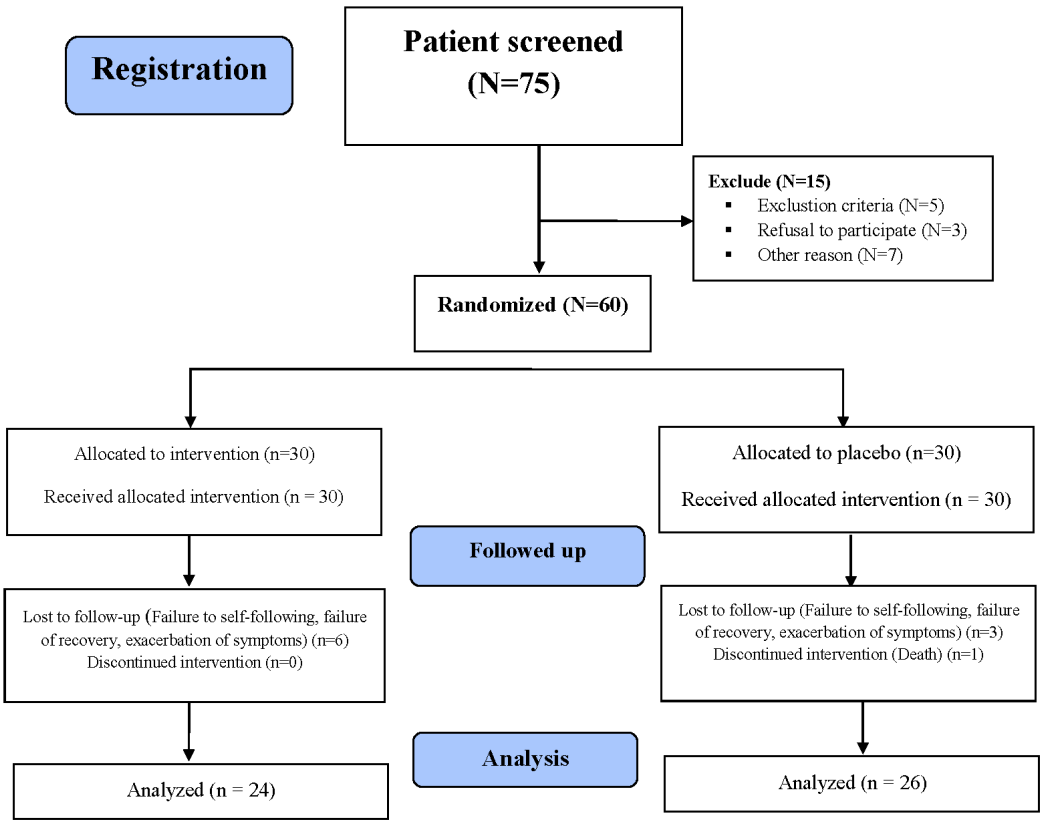

Figure 1. Flow diagram of the study progress through the phases of a parallel randomized trial (CONSORT diagram)

Table 1. The mean ± standard deviations and the percentage of variables in patients with bronchiectasis at the beginning of the study

Variables		Groups of patients with bronchiectasis			p-value
		Placebo Group A (n=26) No. (%)	Symbiotic probiotics Group B (n=24) No. (%)	Total (n=50) No. (%)	
Age (years)		55.73±13.62 (50.23-61.23)	54.5 ±12.59 (49.18-59.82)	55.14±13.02 (51.44±58.84)	0.742*
Gender, n (%)	Male	12(46.2)	7(29.2)	19(38)	0.216**
	Female	14(53.8)	17(70.8)	31(62)	
History of disease, n (%)	Bronchiectasis	26(100)	22(91.7)	48(96)	0.225***
	Other	0	2 (8.30)	2(4)	
Cigarette smoking	Yes	4(15.4)	0	4(8)	0.105***
	No	20(76.9)	23(95.8)	43(86)	
	Quit smoking	2(7.7)	1(4.2)	3(6)	
Drugs used	Inhaled spray	10(38.5)	8(33.3)	18(36)	0.706**
	Inhaled spray and mucolytic agent	16(61.5)	16(66.7)	32(64)	
Duration of disease		7.5(1-17.75)	12(7.75-15)	11.5(2.5-15.25)	0.352 ****
Sputum		24(92.3)	22(91.7)	46(92)	>**0.999***

Notes: *t-test; **Fisher's exact test, ***Chi square; ****Mann–whitney.

Table 2. The rate of pulmonary exacerbations with or without the need for hospitalization in patients with bronchiectasis at the beginning and the end of the study in the placebo group (A), and in the symbiotic probiotic group (B)

Variables			Group of patients			
			Placebo Group A (n=26) No. (%)	Symbiotic probiotics Group B (n=24) No. (%)	*Total (n=50)* No. (%)	*p*-value
At the Beginning of the study	**Exacerbations without hospitalization**	No exacerbation	2(7.7)	2(8.3)	4(8.0)	**0.610*** **
		Once	6(23.1)	6(25)	12(24.0)	
		Twice	14(54.0)	9(37.5)	23(46.0)	
		More	4(15.4)	7 (29.2)	11(22.0)	
	Exacerbations with hospitalization	No Exacerbation	10(38.5)	10(41.7)	20(40.0)	**0.956*** **
		Once	6(23.1)	6(25)	12(24.0)	
		Twice	4(15.4)	4(16.7)	8(16.0)	
		More	6(23.1)	4(16.7)	10(20.0)	
At the end of the study	**Exacerbations without hospitalization**	No Exacerbation	16(61.5)	17(70.8)	33(66.0)	***0.629
		Once	6(23.1)	4(16.7)	10(20.0)	
		Twice	2(7.7)	2(8.3)	4(8.0)	
		More	2(7.7)	1(4.2)	3(6.0)	
	Exacerbations with hospitalization	No Exacerbation	21(80.8)	20(83.3)	41(82.0)	**0.831
		Once	2(7.7)	3(12.5)	5(10.0)	
		Twice	2(7.7)	0	2(4.0)	
		More	1(3.9)	1(4.2)	2(4.0)	

Notes: *Student's t-test; **Fisher's exact test; ***χ2; ****Mann–Whitney U test.

Table 3. The bacterial sputum culture and microbiological pattern of patients with bronchiectasis at the beginning of the study, and at the end of the study in the placebo group (A), and in the symbiotic probiotic group (B)

Variables			Placebo Group A (n=26) N (%)	Symbiotic probiotics Group B (n=24) N (%)	Total N=50	*p*-value
At the beginning of the study	Bacterial sputum culture	Positive	16(61.5)	12(50)	28(56)	0.412**
		Negative	10(38.5)	12(50.0)	22(44.0)	
	Pseudomonas sp.		11(68.8)	5(41.7)	16(57.1)	0.412**
	Enterobacter aerogenes		2(12.5)	4(33.3)	6(21.4)	
	Acinetobacter sp.		2(12.5)	1(8.3)	3(10.7)	
	Citrobacter sp.		0	1(8.3)	1(3.6)	
	Klebciella pnemonia		1(3.8)	1(8.3)	2(7.1)	
At the end of the study	Bacterial sputum culture	Positive	13(50)	12(50)	25(50)	**>0.999*** **
		Negative	13(50)	12(50)	25(50)	
	Pesudomonas sp.		11(84.6)	10(83.3)	21(84)	**>0.999*** **
	Acinetobacter sp.		0	1 (8.3)	1(40)	
	Citrobacter sp.		1(7.7)	0	1(40)	
	Candida sp.		1(7.7)	0	1(40)	

Table 4. HRCT finding of patients with bronchiectasis at the end of the study in the placebo group (A), and in the symbiotic probiotic group (B)

HRCT finding		Placebo Group A (n=21) No. (%)	Symbiotic probiotics Group B (n=20) No. (%)	Total (n=50)	*p*-value
Localized involvement	Yes	0	1(5.0)	1 (2.4)	0.3
	No	21(100.0)	19(95.0)	40(97.6)	
Diffuse involvement	Yes	18(85.7)	16(80)	34(82.9)	0.627
	No	3(14.3)	4(20.0)	7(17.1)	
Right upper lobe (RUL) involvement	Yes	5 (23.8)	5(25.0)	10 (24.4)	0.929
	No	16(76.2)	15(75.0)	31(75.6)	
Right middle lobe (RML) involvement	Yes	8 (38.1)	8 (40)	16 (39)	0.901
	No	13(61.9)	12(60.0)	25(61.0)	
Right lower lobe (RLL) involvement	Yes	12(57.1)	11(55)	23(56.1)	0.890
	No	9(42.9)	9(45.0)	18(43.9)	
Left upper lobe (LUL) involvement	Yes	6(28.6)	3(15.0)	9(22.0)	0.294
	No	15(71.4)	17(85.0)	32(78.0)	
Left lower lobe (LLL) involvement	Yes	7 (33.3)	11(55)	18 (43.9)	0.162
	No	14(66.7)	9(45.0)	23(56.1)	
Lingual involvement	Yes	9(42.9)	4(20.0)	13(31.7)	0.162
	No	12(57.1)	16(80.0)	28(68.3)	
Varicose involvement	Yes	3(14.3)	1(5.0)	4(9.8)	0.317
	No	18(85.7)	19(95.0)	37(90.2)	
Cylindrical bronchiectasis involvement	Yes	5 (23.8)	2(10.0)	7(17.1)	0.240
	No	16(76..2)	18(90.0)	34(82.9)	
Cystic lung lesions	Yes	7(33.3)	5(25)	12 (29.3)	0.558
	No	14(66.7)	15(75.0)	29(70.7)	
Ground glass	Yes	2(9.5)	3(15)	5(12.2)	0.592
	No	19(90.5)	17(85.0)	36(87.8)	
Thickened bronchial wall	Yes	2(9.5)	1(5.0)	3(7.3)	0.578
	No	19(90.5)	19(90.5)	38(92.7)	
Emphysema	Yes	3(14.3)	2(10)	5 (12.2)	0.675
	No	18(85.7)	18(90.0)	36(7.3)	
Pulmonary fibrosis	Yes	2(9.5)	1(5.0)	3(7.3)	0.578
	No	19(90.5)	19(90.5)	38(92.7)	

DISCUSSION

In the current study, we found that the most frequent etiologic pathogen was *Pseudomonas sp.* At the beginning of the study, and after six months, the most common etiologic pathogens of sputum culture were *P. aeruginosa* and some gram-negative organisms in the symbiotic probiotic group (B). This finding was in the line with Weiss et al. researches (22). They found that the consumption of symbiotic probiotics has no change on the sputum pathogens in patients with bronchiectasis (22). Alvarez et al. found that consumption of *L. casei* in young rats led to decreasing of *P. aeruginosa* population in the lungs, led to increasing phagocytic activity of alveolar macrophages and increasing levels of IgA in BAL fluid (23).

Banupriya et al. showed that children who received prophylactic probiotics had a lower incidence of VAP compared to the control group (24). Furthermore, Morrow et al. indicated that patients treated with *Lactobacillus* were significantly less likely to develop microbiologically confirmed VAP compared to patients treated with placebo. They also observed patients treated with probiotics had significantly less *Clostridium difficile*–associated diarrhea than patients treated with placebo (25). On the other hand, Zeng et al. demonstrate that the incidence of microbiologically confirmed VAP in the probiotics group was significantly lower than that in the control patients. Although the incidence rate of clinically diagnosed VAP was higher in control patients (53.0%) than in intervention patients (40.7%), the difference was not statistically significant (26).

We found no difference between symbiotic probiotics and placebo for the rate of pulmonary exacerbations, at the baseline and the end of six month. Also, results showed a decreasing trend in the rate of pulmonary exacerbations with hospitalization (P=0.831) or without hospitalization (P=0.629) among patients who consumed symbiotic probiotics.

In a pilot study, Weiss et al. announced that probiotics may reduce the rate of pulmonary exacerbations, in comparison to the last 2 years and 6 months post-treatment follow-up. However, they found that pulmonary function tests (PFTs), sputum bacteria, neutrophil count, and IL-8 levels have not changed at the end of treatment and during 6 months post-treatment (22).

In a prospective cross-over study, Bruzzese et al. treated 19 patients with *Lactobacillus GG* for 6 months and compared the result with a placebo group. They announced that there was a significant decrease in the rate of pulmonary exacerbations and hospitalization of patients (27).

Knight et al. reported no statistical difference between patients with bronchiectasis who took symbiotic probiotics and patients who took placebo for ventilator-associated pneumonia (VAP) (28).

Although there are many kinds of probiotics produced by pharmaceutical companies, we used LactoCare as a symbiotic probiotic in this study. Of course, other strains may be effective in reducing the rate of pulmonary exacerbations or hospitalization of patients with bronchiectasis.

Recently, the effect of probiotics on inflammatory cells such as Th17 and T_{reg} cells in lung disease has been approved (29). Feleszko et al. found that administration of *Bifidobacterium lactis*, *Lactobacillus rhamnosus GG*, and *Lactobacillus casei* could induce FoxP3 mRNA expression in T_{reg} cells belong to peribronchial lymph nodes (30). Karimi et al. showed that consumption of *Lactobacillus reuteri* led to an increase in the spleen CD^{4+} , CD^{25+} , $FoxP^{3+}$ and T cells (31).

Previous studies have focused on the effects of probiotics consumption in patients who are suffering from respiratory infections such as VAP. Up to now, there has been no sufficient evidence about the effects of probiotics on other respiratory infections such as bronchiectasis (25, 28, 32, 33). Based on the evidence about the effectiveness of probiotics on respiratory diseases, different aspects should be noted for planning research about probiotic prophylaxis. First, specific studies should be conducted regarding the probiotic prevention and treatment of respiratory infections; second, due to different effects of probiotics on immune stimulation, various strains of a probiotic species may be required. Finally, combinations of different microorganisms do not always induce more favorable immune modulation. Overall, probiotics may be

used as an adjunct therapy in bronchiectasis. However, to determine the effective dose of probiotics in bronchiectasis, studies with a larger sample size are necessary.

The current study was conducted in a single center. The sample size of the current study was too small, and statistical tests were not able to identify significant relationships within the data set. To obtain more precise results, it would have been better to base our study on a larger sample size. Also, the sample of the study was not representative of the target population.

CONCLUSION

The probiotics did not effective in the improvement of clinically bronchiectasis, consumption of antibiotics, the rate of pulmonary exacerbations with or without the need for hospitalization, FEV1 and FEV1/FVC, and microbiological pattern. However, to determine the effective dose of probiotics in bronchiectasis, studies with a larger sample size are necessary.

Conflicts of interest

The authors have no conflicts of interests.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Lee AL, Gordon CS, Osadnik CR. Exercise training for bronchiectasis. ***Cochrane Database Syst Rev*** 2021;4(4):CD013110.
2. Metersky ML, Mangardich A. Chronic suppurative lung disease in adults. ***J Thorac Dis*** 2016;8(9):E974-E978.
3. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. ***Respir Med*** 2006;100(12):2183-9.
4. Chalmers JD, Sethi S. Raising awareness of bronchiectasis in primary care: overview of diagnosis and management strategies in adults. ***NPJ Prim Care Respir Med*** 2017;27(1):18.
5. Koser U, Hill A. What's new in the management of adult bronchiectasis? ***F1000Res*** 2017;6:527.
6. Menéndez R, Méndez R, Polverino E, Rosales-Mayor E, Amara-Elori I, Reyes S, et al. Factors associated with hospitalization in bronchiectasis exacerbations: a one-year follow-up study. ***Respir Res*** 2017;18(1):176.
7. de la Rosa D, Martínez-Garcia MA, Olveira C, Girón R, Máiz L, Prados C. Annual direct medical costs of bronchiectasis treatment: Impact of severity, exacerbations, chronic bronchial colonization and chronic obstructive pulmonary disease coexistence. ***Chron Respir Dis*** 2016;13(4):361-71.
8. Guan WJ, Gao YH, Xu G, Lin ZY, Tang Y, Li HM, et al. Characterization of lung function impairment in adults with bronchiectasis. ***PLoS One*** 2014;9(11):e113373.
9. Lesan A, Lamle AE. Short review on the diagnosis and treatment of bronchiectasis. ***Med Pharm Rep*** 2019;92(2):111-6.
10. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn JS, Floto RA, et al. British Thoracic Society guideline for bronchiectasis in adults. ***BMJ Open Respir Res*** 2018;5(1):e000348.
11. Silverman E, Ebright L, Kwiatkowski M, Cullina J. Current management of bronchiectasis: review and 3 case studies. ***Heart Lung*** 2003;32(1):59-64.
12. Doğan R, Alp M, Kaya S, Ayrancioğlu K, Taştepe I, Unlü M, et al. Surgical treatment of bronchiectasis: a collective review of 487 cases. ***Thorac Cardiovasc Surg*** 1989;37(3):183-6.
13. Donovan T, Felix LM, Chalmers JD, Milan SJ, Mathioudakis AG, Spencer S. Continuous versus intermittent antibiotics for bronchiectasis. ***Cochrane Database Syst Rev*** 2018;6(6): CD012733.

14. Kasper D, Harrison TR. Harrison's principles of internal medicine. Vol. 1. McGraw-Hill, Medical Publishing Division; 2005.
15. Vouloumanou EK, Makris GC, Karageorgopoulos DE, Falagas ME. Probiotics for the prevention of respiratory tract infections: a systematic review. ***Int J Antimicrob Agents*** 2009;34(3):197.e1-10.
16. Markowiak P, Śliżewska K. Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. ***Nutrients*** 2017;9(9):1021.
17. De Simone C, Ciardi A, Grassi A, Lambert Gardini S, Tzantzoglou S, Trinchieri V, et al. Effect of Bifidobacterium bifidum and Lactobacillus acidophilus on gut mucosa and peripheral blood B lymphocytes. ***Immunopharmacol Immunotoxicol*** 1992;14(1-2):331-40.
18. Azad MAK, Sarker M, Wan D. Immunomodulatory Effects of Probiotics on Cytokine Profiles. ***Biomed Res Int*** 2018;2018:8063647.
19. Forsythe P. Probiotics and lung diseases. ***Chest*** 2011;139(4):901-8.
20. Kang EJ, Kim SY, Hwang IH, Ji YJ. The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies. ***Korean J Fam Med*** 2013;34(1):2-10.
21. Cangemi de Gutierrez R, Santos V, Nader-Macías ME. Protective effect of intranasally inoculated Lactobacillus fermentum against Streptococcus pneumoniae challenge on the mouse respiratory tract. ***FEMS Immunol Med Microbiol*** 2001;31(3):187-95.
22. Weiss B, Bujanover Y, Yahav Y, Vilozni D, Fireman E, Efrati O. Probiotic supplementation affects pulmonary exacerbations in patients with cystic fibrosis: a pilot study. ***Pediatr Pulmonol*** 2010;45(6):536-40.
23. Alvarez S, Herrero C, Bru E, Perdigon G. Effect of Lactobacillus casei and yogurt administration on prevention of Pseudomonas aeruginosa infection in young mice. ***J Food Prot*** 2001;64(11):1768-74.
24. Banupriya B, Biswal N, Srinivasaraghavan R, Narayanan P, Mandal J. Probiotic prophylaxis to prevent ventilator associated pneumonia (VAP) in children on mechanical ventilation: an open-label randomized controlled trial. ***Intensive Care Med*** 2015;41(4):677-85.
25. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. ***Am J Respir Crit Care Med*** 2010;182(8):1058-64.
26. Zeng J, Wang CT, Zhang FS, Qi F, Wang SF, Ma S, et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. ***Intensive Care Med*** 2016;42(6):1018-28.
27. Bruzzese E, Raia V, Spagnuolo MI, Volpicelli M, De Marco G, Maiuri L, et al. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study. ***Clin Nutr*** 2007;26(3):322-8.
28. Knight DJ, Gardiner D, Banks A, Snape SE, Weston VC, Bengmark S, et al. Effect of synbiotic therapy on the incidence of ventilator associated pneumonia in critically ill patients: a randomised, double-blind, placebo-controlled trial. ***Intensive Care Med*** 2009;35(5):854-61.
29. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. ***Annu Rev Immunol*** 2009;27:485-517.
30. Feleszko W, Jaworska J, Rha RD, Steinhausen S, Avagyan A, Jaudszus A, et al. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. ***Clin Exp Allergy*** 2007;37(4):498-505.
31. Karimi K, Inman MD, Bienenstock J, Forsythe P. Lactobacillus reuteri-induced regulatory T cells protect against an allergic airway response in mice. ***Am J Respir Crit Care Med*** 2009;179(3):186-93.
32. de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al. Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial. ***Vaccine*** 2006;24(44-46):6670-4.
33. Stojković A, Simović A, Bogdanović Z, Banković D, Poskurica M. Clinical trial/experimental study (consort compliant): Optimal time period to achieve the effects on synbiotic-controlled wheezing and respiratory infections in young children. ***Srp Arh Celok Lek*** 2016;144(1-2):38-45.