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**Are probiotics effective at reducing the symptoms of asthma in children from birth to twelve-years old?**

Rachel Sulat, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirement for

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**OBJECTIVE:** The objective of this systematic review is to determine whether or not probiotics are effective at reducing the symptoms of asthma in children ages birth to twelve-years old.

**STUDY DESIGN:** Review of three English-language, double-blinded randomized controlled trials (RCTs) from 2010 and 2011.

**DATA SOURCES:** Three peer-reviewed RCTs were found using PubMed database. These studies compared probiotics to placebos in patients with episodes of wheezing.

**OUTCOMES MEASURED:** Reduction in symptoms of asthma (particularly wheezing) measured with the use of diary cards and symptom scores.

**RESULTS:** Chen et al. demonstrated statistically significant improvement in daytime asthma symptoms in probiotic treated versus placebo treated children age 6–12 years, with a p value of 0.01. Rose et al found no statistically significant difference in asthma related symptoms between probiotic and placebo groups in children age 6–24 months. A Mann-Whitney U-test was used to determine this fact, using a 95% confidence interval. No test statistic was given. Van der Aa found that a synbiotic mixture containing a probiotic to reduce wheezing and/or noisy breathing apart from colds compared to placebo. This reduction was statistically significant, with a 95% confidence interval and a p value of 0.001.

**CONCLUSIONS:** These results suggest that probiotics are effective at reducing asthma symptoms such as wheezing. Two of the three studies suggested statistically significant improvement in probiotic treated versus control groups.

**KEY WORDS:** probiotics, asthma, wheezing.

## INTRODUCTION

Asthma is a chronic inflammatory airway disorder characterized by episodic wheezing, difficulty breathing, chest tightness, and cough.<sup>1</sup> While the exact cause of this disorder is unknown, there are several risk factors that have been identified. These include obesity, allergens, environmental irritants such as tobacco smoke, and precipitating factors such as exercise, respiratory tract infections, gastroesophageal reflux, and medications such as aspirin, among others. The strongest identified predisposing factor, however, is atopy- a genetic tendency to develop allergic disease.<sup>1</sup>

Asthma is a common disease, affecting approximately 7-10% of the population.<sup>1</sup> In 2009, this percentage accounted for 24.6 million Americans.<sup>2</sup> Because it affects so many individuals, the costs of this disorder are also significant. The total medical expenditures were estimated to be \$62.8 billion in the United States in 2009.<sup>2</sup> In addition, asthma can vary in severity; a severe exacerbation can be life-threatening, requiring hospitalization and significant medical attention. Each year, asthma accounts for roughly 500,000 hospital admissions and 4,500 deaths in the United States. Furthermore, over the past twenty years in the United States, the prevalence of, hospitalizations for, and fatalities due to asthma have all increased.<sup>1</sup>

As it can be seen, asthma is a significant disorder and thus is important to understand. Much research has been done and a lot is known about asthma. It is known that asthma is an inflammatory airway disorder. Inflammatory cells, such as eosinophils, neutrophils, and lymphocytes (especially T lymphocytes), infiltrate the mucosa of the lower airways.<sup>1</sup> Goblet cell hyperplasia is also seen, leading to increase mucus production. The excess mucus can cause plugging of the small airways.<sup>1</sup> Bronchial smooth muscle hypertrophy and mucosal edema may be present, leading to further obstruction and narrowing of the airways.<sup>1</sup> These pathologic

changes to the airway, if significant, will lead to symptoms, including dyspnea, wheezing, and chest tightness. These symptoms may vary in frequency and severity, ranging from brief infrequent occurrences to almost continuous symptoms.<sup>1</sup>

While there is quite a bit that is known about asthma, there is other information that has yet to be discovered. For instance, the exact cause of asthma is unknown. As discussed above, many risk factors and predisposing features are associated with asthma, the strongest of which is atopy. However, the exact trigger to begin this inflammatory process is not completely understood. Additionally, the severity of inflammation is not always correlated with the severity of symptoms. It is not yet known, then, what can account for this discrepancy.<sup>3</sup>

Due to the extensive research of the pathogenesis of asthma, there are many treatment options aimed at combating these processes to reduce symptoms. The gold standard of treatment is not necessarily one medication; instead, a stepwise approach is often applied. All patients are given a short-acting beta-2-agonist (SABA), such as albuterol. These agents are intended to be used as needed in the event of an asthma attack, when prompt control is necessary.<sup>1</sup> For persistent asthma, an inhaled corticosteroid (ICS) is first line. These agents, such as budesonide, work at reducing both acute and chronic inflammation.<sup>1</sup> If the ICS alone does not control the patient's asthma, the dose can be adjusted or a long-acting beta-2-agonist (LABA) may be added.<sup>1</sup> A LABA, such as formoterol, works at long term prevention of asthma symptoms.<sup>1</sup> Further treatment may be required when prompt control of asthma is needed in the event of a severe attack; in this case, systemic corticosteroids are often used.<sup>1</sup> Additionally, several agents have been developed with the intention of preventing further pathologic changes and thus at preventing asthma. These include leukotriene modifiers, mast cell activators, and agents like Omalizumab, which works based on the allergic nature of asthma.<sup>1</sup>

This allergic nature of asthma is precisely what this review is aimed at investigating. One hypothesis for the increasing prevalence of asthma is related to the hygiene hypothesis, which states that diminished microbial exposure in today's society of avid hand washing and antimicrobial hand sanitizer use has led to an altered intestinal micro biota (which is believed to account for a significant part of human immunity).<sup>6</sup> Therefore, the three randomized controlled trials (RCTs) reviewed in this paper examine asthma symptom reduction by increasing colonization of intestinal micro-organisms through the use of probiotics given to young children.<sup>6</sup> Because atopy is noted to be the most important predisposing factor in the development of asthma, the implications of a method that targets the allergic nature of the disorder are significant.

## OBJECTIVE

The objective of this systematic review is to determine whether or not probiotics are effective at reducing the symptoms of asthma in children ages birth to twelve-years old.

## METHODS

Specific criteria were used when selecting the studies for this review. The populations examined were limited to children younger than twelve years old with diagnosed asthma or diagnosed episodes of wheezing. All studies included an intervention of probiotics; these included *Lactobacillus gasseri*, *Lactobacillus rhamnosus*, and a synbiotic containing the probiotic *Bifidobacterium breve*. In these studies, the experimental groups receiving the probiotics were compared to a control group receiving a visually matched placebo. The outcomes measured were reduction in the symptoms of asthma. The three studies classified symptoms of asthma in various ways, but this review will focus on the symptom of wheezing. Wheezing was evaluated either by rating severity on a scale of 1-4 or by tracking symptom severity with the use

of diary cards. All three studies included in this review are double-blind placebo-controlled randomized clinical trials (RCTs).

Key words used in searches to find these three studies included “asthma,” “probiotics,” and “children.” All articles were published in English and in peer reviewed journals. They were researched by the author using the PubMed database. These articles were selected based on their relevance to the clinical question and that the outcomes measured were patient oriented.

Inclusion criteria included studies that were randomized controlled trials published after 2007, that included subjects less than 12 years old and had asthma or episodes of wheezing. Exclusion criteria comprised studies with patients older than 12 years of age and articles that focused exclusively on disease oriented evidence, such as IgE levels or spirometry. The statistics that were used and reported are RRR, ARRR, RBI, ABI, NNT, p-value, and CI.

Table 1- Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Chen et al., 2010	RTC	118	6-12 yrs	Age 6-12 years with a history of 2 or more episodes of wheezing within the last 6 months and diagnosed mild-moderate persistent asthma. Persistent AR diagnosed for four or more days per week and for more than 4 weeks prior to the recruitment of the patients.	Pts previously treated with immunotherapy, oral or parenteral corticosteroids administered for more than 15 consecutive days or inhaled $\beta$ 2-agonists more than 4 times a day Suffering from other respiratory diseases	11	<i>Lactobacillus gasseri</i> 1 capsule twice a day x 8wks

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Rose et al., 2010	RTC	131	6 - 24 mo	a history of at least two physician-diagnosed episodes of wheezing ( $\geq 3$ days, necessitating $\beta_2$ -bronchodilators or steroids) during the past 12 months  at least one of these exacerbations in the 3 months immediately before enrolment  a first-degree family history of atopic disease	<ul style="list-style-type: none"> <li>•preterm birth (&lt;37 weeks of gestational age)</li> <li>•congenital malformations</li> <li>•systemic disorders and chronic diseases</li> <li>•current antibiotic therapy</li> <li>•prior exposure to and known intolerances towards ingredients of probiotics</li> </ul>	29	<i>Lactobacillus rhamnosus</i> Capsules twice daily x 6 mo
Van der Aa et al., 2011	RTC	90	< 7 mo	<ul style="list-style-type: none"> <li>•SCORing Atopic Dermatitis (SCORAD) score &gt;15</li> <li>•exclusive formula feeding at time of enrolment</li> </ul>	<ul style="list-style-type: none"> <li>•other major medical problems</li> <li>•use of probiotics or immunomodulatory medication during the 4 weeks before enrolment</li> </ul>	15	Synbiotic containing <i>Bifidobacterium breve</i>  Given in an whey-based formula x12 wks

## OUTCOMES

The outcomes measured were wheezing and the severity of asthma symptoms. All studies used diary cards completed by the children's parents. In two of the three studies, the number of wheezing episodes per day and the number of days with a wheeze were recorded on the diary cards in order to assess severity.<sup>5,6</sup> One of the three studies had parents complete diary cards

documenting asthmatic scores and rating asthma symptoms on a 4 point scale, such that 0= no symptoms, 1= mild symptoms, 2= moderate symptoms, and 3= severe symptoms.<sup>4</sup>

## RESULTS

Three randomized controlled trials evaluated the effect of probiotics on symptoms of asthma. All three studies examined these effects in children younger than 12 years old; two of these studies included infants (< 7 months and 6–24 months) and the third studied children age 6–12 years. Additional inclusion criteria can be found in Table 1. The studies also set exclusion criteria, such as concurrent medical disorders, especially other respiratory disorders, and recent asthma medication use, among others (Table 1).<sup>4,6</sup> These criteria help to eliminate confounding variables when analyzing the data results, such that wheezing and wheeze reduction could not be attributed to other factors.

None of these studies reported issues with patient compliance in taking probiotics. All studies lost some participants to follow up, however. In Chen et al, there was a 9.5% drop out rate, 17% in Van der Aa, and 22% in Rose et al. The latter is a relatively high rate and may have an influence on validity of results. However, in all three studies, an intention to treat analysis was completed.

In the Chen et al double-blind, randomized, placebo-controlled study, children age 6–12 years old with mild persistent asthma were enrolled. A computer randomization schedule was made placing all participants into either the probiotic treated (55) or placebo group (61). Patients in the treatment group received one capsule of *L. gasseri* twice a day and the control group received a placebo capsule (containing milk powder) twice a day, for eight weeks. Every two weeks, participants' clinical symptoms were evaluated by a physician. Patients also kept symptom diary cards which rated symptoms on a 4 point scale (explained above). A paired t-test

was used to assess changes from baseline, with a p-value below 0.05 considered significant. Of the 116 patients that were allocated to study groups, 105 were analyzed (9.5% loss to follow up).<sup>4</sup>

A statistically significant improvement rate was found in the probiotic treated group for daytime asthmatic symptoms. Of the probiotic treatment group, 37 out of 49 reported improvement in daytime asthmatic symptoms, an experimental event rate (EER) of 75.5%. The placebo group had a control event rate (CER) of 62.5% (Table 2). This is a statistically significant difference, with a p-value of 0.01. This result has a relative benefit increase (RBI) of 20.8% and an absolute benefit increase (ABI) of 13% (Table 2). The number needed to treat (NNT) is 8; thus, for every 8 patients given probiotics, 1 more will have improvement in daytime asthma symptoms than placebo, over 8 weeks (Table 2).<sup>4</sup>

Table 2- Treatment Effect of *L. gasseri* on Daytime Asthma Symptoms

CER	EER	RBI	ABI	NNT	p-value
62.5%	75.5%	20.8%	13%	8	0.01

In the Rose et al study, children age 6–24 months were recruited from a walk-in clinic over the course of a year (to exclude seasonal selection bias). Patients were observed for three months to confirm selection criteria, and then randomly assigned to a placebo (66 children) or experimental (65 children) group. The experimental group received *L. rhamnosus* capsules twice a day for six months. These capsules were matched to the placebo for size, shape, and volume. The probiotic was given in a double-blind matter. Patients were clinically monitored for one year. Asthma severity was assessed with symptom diaries kept by parents that recorded episodes of asthmatic exacerbations, including wheeze. Statistical analysis was done using the Mann-

Whitney U-test for normally distributed variables on asthma related events, such as days with wheeze. The authors do not give a test statistic, but they state that the test revealed no statistical significance. Median values are given +/- a 95% confidence interval, such that  $p < 0.05$  is considered statistically significant. For “days with wheeze” during the six month follow up period after intervention had taken place, patients in the probiotic group had a median of 8 days and patients in the placebo group had a median of 11 days with a wheeze. However, as previously stated, this was not found to be statistically significant.<sup>5</sup> Additionally, in certain subgroups analyzed, it was even found that the treatment group had statistically significant lower asthma symptom scores.<sup>5</sup>

The van der Aa et al. study was a randomized double-blind study. Participants were ninety full-term infants < 7 months old. These infants were randomized using computer generated lists to receive either a hydrolyzed whey-based formula containing a synbiotic (combination of probiotic *Bifidobacterium breve* and short-chain galactooligosaccharides and long chain fructooligosaccharides) (46 infants) or the same formula without the synbiotic (44 infants). The formula was given on demand, for a period of 12 weeks. Participants followed-up one year after the start of the study, at which time parents were asked about respiratory symptoms and medication use through the use of a validated questionnaire.<sup>6</sup>

Analysis of all data was done with an unpaired t-tests for parametric data, and the Mann-Whitney U-test for nonparametric data. The analysis showed that “wheezing and noisy/rattly breathing apart from colds”<sup>6</sup> was significantly less prevalent in the synbiotic treated group compared with the placebo group. Because this study involved infants that did not yet have a diagnosis of asthma, the results reflect a prevention effect rather than treatment. At the time of follow up, the experimental event rate (EER) was 2.8%, and the control event rate (CER) was

30.8%. This translates to a relative risk reduction (RRR) of – 91% and an absolute risk reduction (ARR) of -28% and thus a NNT of -3 (Table 3). This means that 3 patients would need to use this synbiotic formula in order to prevent one less instance of wheezing/noisy breathing apart from colds. The p-value for this data is 0.001 with a 95% confidence interval. Because the NNT is low and the p-value is <0.05, this demonstrates that the synbiotic was effective at preventing wheezing in a statistically significant manner.<sup>6</sup>

Table 3- Prevention of Wheezing and Noisy/Rattly Breathing Apart from Colds

CER	EER	RRR	ARR	NNT	95% CI (-43.4 to -12.5 for ARR)
30.8%	2.8%	-0.91	-0.28	-3	p-value= 0.001

## DISCUSSION

This systematic review analyzed three RCTs to determine if probiotics were effective at reducing symptoms of asthma, particularly wheezing. One of these three studies showed no improvement in asthma symptoms.<sup>5</sup> The other two demonstrated statistically significant reduction in wheezing;<sup>4,6</sup> however they did so in specific circumstances that may not be applicable universally. Therefore, additional research is needed before strong recommendations for this patient population can be made.

Probiotics have been used as adjunctive treatment in several other disorders of the intestinal tract, such as infectious diarrhea, irritable bowel syndrome, *H. pylori* infection, *C. difficile* infection, and preventions of vulvovaginal candidiasis. As such, several products are readily available in the United States.<sup>7</sup> However, these are all off-label indications; the FDA has not approved probiotics for any therapeutic indications. Probiotics are classified as dietary supplements, and therefore do not require FDA approval for use as such.<sup>8</sup>

There are some standard contraindications and warnings associated with probiotics, as there are with any medical intervention. Patients with a hypersensitivity to microorganisms, or to lactose or milk, should not take probiotics.<sup>7</sup> Also, they should not be used in immunocompromised patients, patients with central venous catheters, or patients with a high fever.<sup>7</sup>

Since probiotics are readily available with few contraindications, the findings of this systematic review can be useful for patient populations fitting the criteria of the clinical question. However, there are other limitations of the studies reviewed to consider. In Chen et al., patients continued to use asthma medications throughout the study. Although this occurred in both experimental and control groups, and researchers attempted to account for it with the use of medication record scores, it still must be considered.<sup>4</sup> Additionally, the authors point out that any research regarding allergic disease and probiotics may have varied results due to variations in host factors such as genetic predisposition, and environmental factors such as diet and individual microflora.<sup>4</sup> Randomization helps limit the effect of such variables but cannot eliminate them completely.

Rose et al. found no beneficial effect of probiotics on asthmatic symptoms. Some limitations of this study were that the results relied on caretakers' evaluation of the children's symptoms on diary cards, since the children were 6–24 months of age.<sup>5</sup> Additionally, by chance, the randomization placed a statistically significant greater amount of children experiencing more than 5 episodes of wheezing per year, as well as more children with household exposure to cigarette smoke, into the experimental vs the control group.<sup>5</sup> This may have skewed the data. Lastly, as previously mentioned, there was a loss to follow up of 22%.<sup>5</sup> This too may affect the results of the study and brings to question the reliability of the findings.

In the van der Aa study, one limitation for this systematic review is that this investigation examined a probiotic that was included as part of a synbiotic mixture containing additional prebiotic components;<sup>6</sup> this is therefore a confounding variable and complicates the application of the results to the probiotic's effect alone. This study too relied on parents completing diary cards, and they may have misunderstood the term "wheeze."<sup>6</sup> However this is likely to have occurred in both groups and thus is not likely to be substantially influence the results.

## CONCLUSION

This review has shown probiotics to be effective at reducing asthma symptoms. Majority (two of three) of studies showed reduction; however the third failed to, and even saw worse symptoms in the probiotic group than in the placebo group. Additionally, other factors complicate the data analysis, such as the concurrent use of a prebiotic in the van der Aa study and the statistically significant difference in wheeze before probiotics in the Rose et al. study. Therefore, further research needs to be done before probiotics should be considered as a means of prevention or treatment of asthma symptoms such as wheeze. This research may include studies that examine exclusively probiotics, and most optimally the same strain of bacteria; for instance, several studies examining only the effect of one *Lactobacillus* strain would be of more use. If these studies were to continue to show probiotics as effective, additional studies comparing *Lactobacillus* versus *Bifidobacterium* would also be of interest. Regardless, the involvement of microflora in the development of allergic disease appears to have validity and is an intriguing area of continued investigation.

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