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Synbiotic or Zinc supplementation in the treatment of children with bacterial pneumonia, a double-blinded randomized clinical trial

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Abstract

Background: There is disagreement about the use of zinc and synbiotics in improving the effectiveness of antibiotics in the treatment of bacterial pneumonia in children or reducing the side effects of this treatment. The aim of this study was to evaluate the interventional effects of synbiotics and zinc sulfate on reducing clinical symptoms and the average duration of treatment in children suffering from bacterial pneumonia.

Methods: This study was a randomized clinical trial with a parallel-group. The participants included 1 month to 18 years children who were admitted to Sabzevar Heshmatieh Hospital with fever, cough, and respiratory distress with a diagnosis of bacterial pneumonia. They were assigned to the three groups of antibiotic only, antibiotics/synbiotics and antibiotics/zinc, randomly. Clinical symptoms including fever, faster respiration rate per minute (Tachypnea), retraction (subcostal, intercostal, suprasternal, and nasal flaring), crackles, wheezing, cough, and gastrointestinal side effects (diarrhea) were recorded on arrival and daily until discharge and compared at a significance level of 0.05.

Results: Overall, there was no significant difference between the patients' clinical symptoms (fever, respiration rate per minute, subcostal, intercostal and suprasternal retraction, and nasal flaring), crackles, wheezing, cough, and gastrointestinal side effects (diarrhea) in the three groups.

Conclusion: The results of this study could not show any clinical benefit for prescribing zinc or synbiotics in combination with standard antibiotic therapy in the treatment of children and infants, and they could not reduce the side effects of this treatment.

Key Words: Children, Infants, Pneumonia, Prebiotics, Probiotics, Zinc.

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1- INTRODUCTION

Pneumonia is an inflammation of the lung parenchyma that is most often caused by microorganisms. However, many non-infectious causes such as food aspiration, stomach acid, foreign body, hydrocarbons, and allergic reactions can also cause pneumonia (1). Pneumonia is the most common cause of death in children worldwide, especially in developing countries, and each year causes about 4 million deaths among children (2-4). Annually, 1.5 to 2.5 percent of infants under one year of age and 3 to 4 percent of children under 5 suffer from pneumonia in the United States. The World Health Organization (WHO) estimates that 4 million deaths from pneumonia occur among children annually, with half of these deaths occurring in children under one year of age (5, 6). It is reported that the most common season of pneumonia is winter and risk factors such as the history of asthma in children, parental smoking in the child's environment, poor economic situation, use of fossil fuels at home, and indoor or outdoor air pollution are predisposing factors increasing pneumonia (7, 8). The most common bacterial agent in children between the ages of 3 weeks and 4 years is Streptococcus pneumonia (pneumococcus). In children with 5 years of age or older, Mycoplasma pneumonia and Chlamydia pneumonia are the most common bacterial pathogens. Streptococcus pneumonia, Haemophilus influenzae, and Staphylococcus aureus are the leading causes of hospitalization and death from bacterial pneumonia in children in developing countries (9).

Respiratory infections, especially lower respiratory tract infections such as bronchitis and pneumonia, have multiple and sometimes irreversible effects on the health system; and the economic and social effects of these infections are among the most important challenges of public health because it causes high costs of treatment and hospitalization, absenteeism from school, and loss of working days on the side of the parents (10).

A wide range of etiological factors, widespread inappropriate use of antibiotics, increased bacterial resistance, lack of access to vaccines for many viruses and bacteria challenge the effective and appropriate treatment of this disease (11, 12). This has reduced the sensitivity to common antibiotics and created multidrug resistance in children (13). Today, in addition to attempts to introduce the next generation of antibiotics to counteract this resistance, the use of new therapies such as the simultaneous use of synbiotics or zinc has been considered.

Since the introduction of probiotics by Metchnikoff in the early 1990s, these compounds have been increasingly considered in improving the function of various body systems. According to the World Health Organization (WHO), and the Food and Agriculture Organization of the United Nations (FAO), probiotics are living microorganisms that when consumed in sufficient quantities as part of the food, have beneficial effects through the intestinal flora on the health of the host. These compounds are classified by the Food and Drug Administration as GRAS[2] compounds and are used in children's food formulations in some developed countries. Different strains of probiotic microorganisms can be used in any dose alone or in combination with other beneficial health supplements (prebiotics and vitamins), or antibiotics (14).

Probiotics regulate the microbial flora of the small intestine or regulate microbiota in other parts of the human body. They improve systemic and local immunity and compete with invasive pathogens and recover microorganisms that ensure the safety and health of the host. Numerous

[2] Generally Recognized As Safe

studies show the benefits and safety of using probiotics in childhood (15, 16). The effects of probiotics taken together with antibiotics on the prevention and treatment of antibiotic-related diarrhea in children with pneumonia have not been fully investigated (14, 17). This could provide a good opportunity to study the effect of the simultaneous prescription of probiotics with antibiotics in the treatment of bacterial pneumonia in children. Absolutely, one of the aspects of the use of probiotics that is considered today is their ability to prevent ventilator-associated pneumonia (18). There is serious disagreement about the role of this supplement in the prevention of Hospital-acquired infection or nosocomial infection (19) because there is evidence of Septicemia following probiotic treatment, especially in the field of immune deficiency or prematurity (20, 21).

Malnutrition is associated with an increased prevalence and severity of pneumonia and plays an important role in pneumonia mortality. The possible mechanism of this effect is a decrease in the immune capacity that occurs during malnutrition. Decreased immune capacity in malnourished children may be due to zinc deficiency, which in particular leads to impaired cellular immunity (22-24). There is strong evidence for an association between zinc deficiency and childhood infections. Adequate zinc supplementation has been shown to significantly reduce the prevalence of lower respiratory tract infections and diarrhea (25-27). In developing countries, daily oral zinc (10 mg for children under 12 months, and 20 mg for children of 12 months and older) has been reported to reduce mortality from severe clinical pneumonia (1). However, to date, no comprehensive study has been performed on the effect of antibiotic-administered zinc on reducing clinical symptoms and length of hospital stay in children with bacterial pneumonia. In addition to investigating the interventional effect of oral synbiotics, this could provide a good opportunity to reduce the clinical symptoms and speed up the treatment of children with bacterial pneumonia. The aim of this study was to evaluate the interventional effects of synbiotics and zinc sulfate on reducing clinical symptoms and the average duration of treatment in children with bacterial pneumonia.

2- MATERIALS AND METHODS

2-1. Study design and population

This study was a randomized clinical trial with a parallel-group in which infants and children with emergency or elective hospitalization in Heshmatieh Hospital in Sabzevar were diagnosed with pneumonia in the autumn of 2019 as well as the winter and spring of 2020. Infants and children between the ages of one month and 18 years, based on clinical, radiographic, and laboratory findings, including left shift leukocytosis or high ESR[3] and CRP[4]or lung involvement on radiography, with a diagnosis of moderate up to very severe bacterial pneumonia, isolated from patients with atypical and viral pneumonia were included in the study. The exclusion criteria were having a history of underlying diseases such as cystic fibrosis, immunodeficiency, chronic heart disease, developmental disorders, failure to thrive, and legal guardianship dissatisfaction. Furthermore, if the patient refused to complete the treatment and any side effects occurred during the study, he/she was excluded from the study.

The sample size was estimated at 41 people based on similar studies and taking into account the means of 32 and 40, the standard deviations of 3 and 4, $\alpha = 0.05$, and $\beta = 80\%$; and taking a 10% drop in the number of people in each group the sample size was determined as 45 people.

[3] Erythrocyte Sedimentation Rate

[4] C-reactive protein

Available sampling was performed among patients referred to Heshmatieh Hospital. The assignment of patients to study groups was done by permutation block randomization with 1: 1: 1 blocks.

The procedure was as follows: the letters A, B, and C were removed from the envelope by drawing lots and were accidentally removed from the envelope, and then the other patients were assigned to the groups by fixed permutations (according to the referral number). In this study, the researcher and the physician treating the patient (as the person evaluating the response to treatment) were unaware of the study groups and this study was a double-blind clinical trial.

2-2. Methods

The three groups of the study included: The first group (control group) received antibiotic treatment alone for at least 5-7 days. The mentioned antibiotic treatment protocol was also performed in the second and third interventional groups. The second group received antibiotics (similar to the first group), along with synbiotics. The type, amount, and method of taking synbiotics varied according to the age of the child. For children under two years of age, 5 drops of PediLact oral drops made by Zist Takhmir Company were used daily for 5 days. The 15 ml oral probiotic drops contain probiotic strains of 10^9 CFU[5] and prebiotic fructooligosaccharides. For children over 2 years old, KidiLact synbiotic made by Zist Takhmir Company was used 1 sachet daily for 5 days, which was consumed with water, juice, or milk according to the patient's taste, 2 to 4 hours after antibiotic taking. KidiLact contains high levels of 7 strains of probiotic bacteria (10^9 CFU)[6], including the pediatric Bifidobacterium infantis strain, along with the prebiotic fructooligosaccharide. The third group received a prescription of antibiotics (similar to the first group), along with zinc sulfate syrup. The dose of 10 mg/day elemental zinc was used for children under 1 year, and 20 mg/day for children over 1 year for 5 days.

To assess the outcome, the patients' clinical symptoms including fever, the respiratory rate per minute to diagnose tachypnea, retraction (subcostal, intercostal, suprasternal), nasal flaring, crackles, wheezing, cough, and gastrointestinal side effects such as diarrhea were evaluated through examination, by a person who was not aware of the type of treatment. Results of the examination were recorded in the relevant table on arrival and daily until discharge.

2-3. Ethical Consideration

The used method was approved by the ethics committee of Sabzevar University of Medical Sciences with the code IR.MEDSAB.REC.1398.072 and its protocol was registered in the Iranian trial system (IRCT20190611043869N1). Written informed consent was obtained from the children's legal guardians prior to enrollment.

2-4. Statistical Analysis

Mean (standard deviation) was used to describe quantitative variables in terms of conditions, and frequency report (percentage) was used for qualitative variables. Chi-square test or Fisher's exact test was used to compare qualitative factors between the study groups. Then, if normal, to compare the mean of the quantitative outcomes among the three groups, analysis of variance was used and if the data were not normal, its

[5] *Bifidobacterium infantis, Lactobacillus rhamnosus, Lactobacillus reuteri*

[6] *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium infantis, Bifidobacterium breve, Streptococcus thermophilus*

nonparametric equivalent, Kruskal-Wallis, was performed. For data analysis, SPSS software version 14 was implemented, and the value of P-value <0.05 was considered statistically significant.

3- RESULTS

A total of 135 people were randomly assigned to the three study groups (Chart 3-1). At research baseline, no significant difference was observed among the basic characteristics of patients in terms of gender (p = 0.811), white blood cell count (p = 0.120), neutrophil (p = 0.071), ESR level (p = 0.422), body temperature (p = 0.818), the number of breaths (p = 0.159) and the type of lung lesion in chest x-ray (p = 0.710) (**Table 1**). The CONSORT diagram shows the phases of investigation progress on the patients entering the study (**Fig. 1**).

The studied groups were not significantly different in terms of the changes in body temperature and respiration rate of the patients in different age ranges, in any of the compared intervals. (**Figures 2** and **3**)

The studied groups were not significantly different in terms of the different clinical symptoms in different age ranges (**Tables 2-6**).

The mean duration of hospitalization in patients in the antibiotic group was 5.7±0.75 days; in patients in the antibiotic group with synbiotics it was 6.1 ± 1.4 days, and in patients in the antibiotic group with zinc it was 5.9± 1.3 days. No significant difference was found among the means of the studied groups (p = 0.192).

Table-1: Characteristics of the patients

Variables	AB SD ± mean	AB + PB SD ± mean	AB + Zn SD ± Mean	P Value
Leukocytes ($\times 10^3$)	15 ± 2	17 ± 5	16 ± 3	0.120
Neutrophils (%)	64.4±10	69.4 ± 8	66.9 ± 10	0.071
ESR (mm/hr)	45.6±13	45.9 ± 23	50.7 ± 21	0.422
Fever (C°)	38.8±36.6	38.8 ± 0.51	38.7 ± 0.53	0.818
Respiratory Rate (n/min)	47.3±12	51.1 ± 13	52.2 ± 12	0.159
Sex (frequency %)				
Male	25(55.6)	26(57.8)	2(51.1)	0.811
Female	20(44.4)	19(42.2)	22(48.9)	
Chest Radiography				
Normal	1(2.2)	3(6.7)	3(6.7)	
Lobar density	38(84.4)	38(84.4)	39(86.7)	0.071
Other	6(13.3)	4(8.9)	3(6.7)	

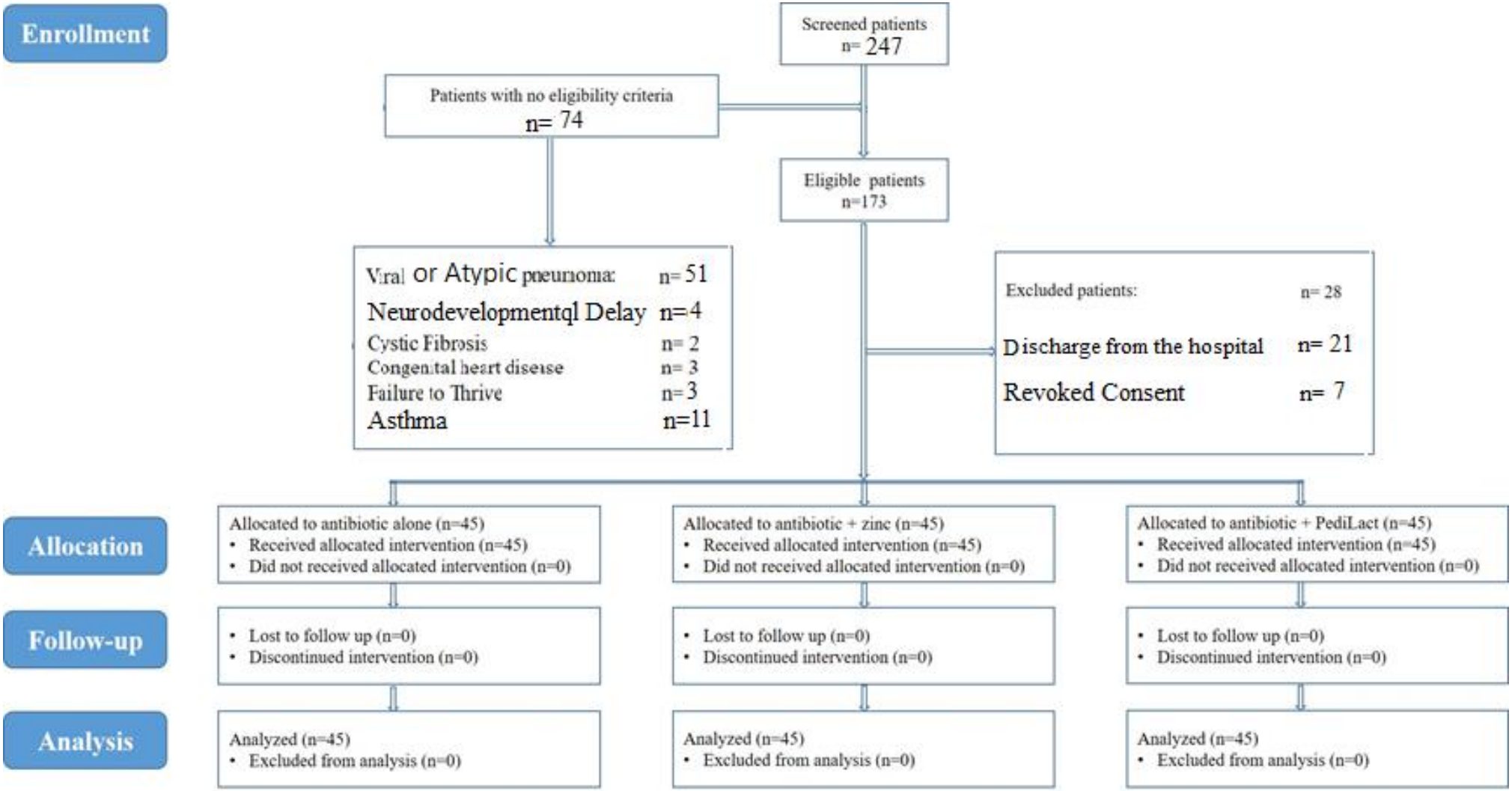

Fig. 1: CONSORT chart on the phases of investigation progress on the patients entering the study

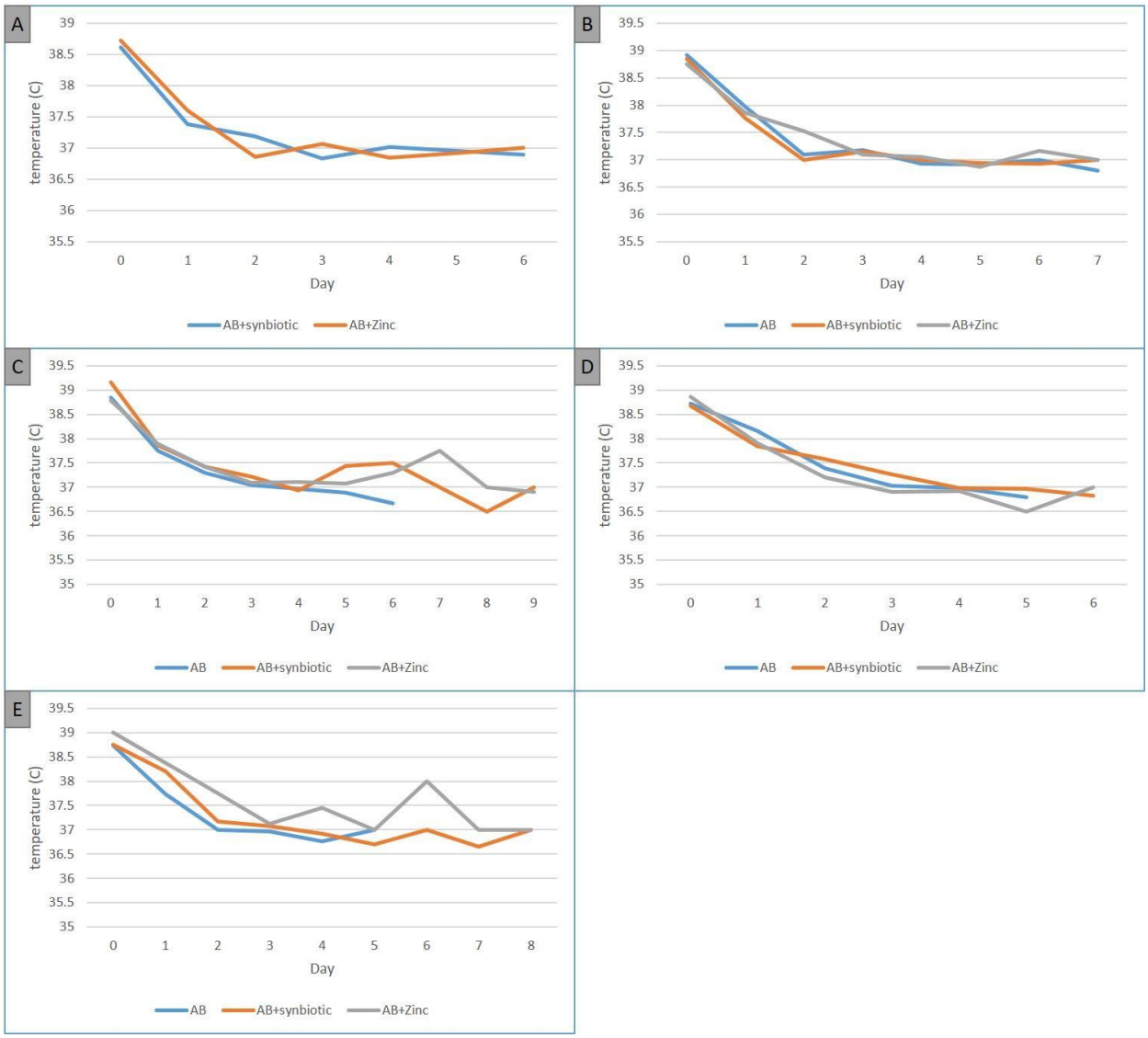

Fig. 2: Overall Body temperature changes in different age ranges, A: 1-3, B: 3-12, C: 12 - 36, D: 36 – 72, and E: 72 - 120 months.

4- DISCUSSION

The results of the present study revealed that except for a significant reduction in the number of breaths as well as wheezing in the middle of the intervention process in the antibiotic group only [number of breaths: on the first, third, fourth, and fifth day and wheezing on the first day], other clinical symptoms of the patients including fever, subcostal retraction, intercostal retraction, suprasternal retraction, nasal flaring, crackles, wheezing and cough along with gastrointestinal side effects (diarrhea) were the same among the study groups at different times.

In a clinical trial, Bagri et al. (2017) examined 476 children aged 2-24 months with pneumonia in one of the groups of antibiotic treatment alone or antibiotics in combination with zinc. In this study, as in the present study, the researchers did not report any significant clinical benefit for adding zinc to the antibiotic regimen of children with pneumonia, although they reported a non-significant tendency to early recovery for patients receiving zinc (28).

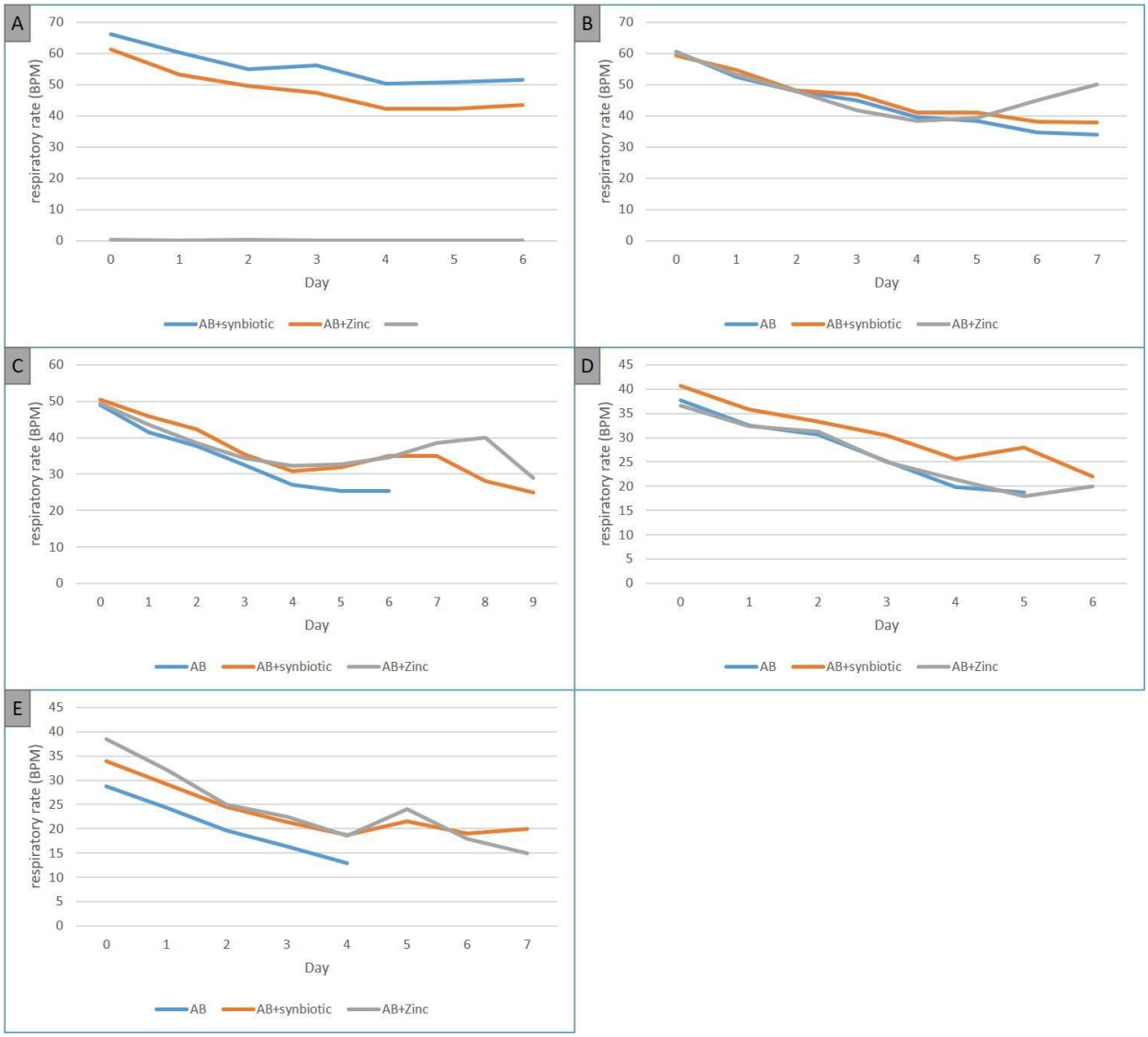

Fig. 3: Changes in the respiration rate in different age ranges, A: 1-3, B: 3-12, C: 12 - 36, D: 36 – 72, and E: 72 - 120 months.

In another study, consistent with the results of the present study, Bose et al. (2006) did not confirm the beneficiality of adding zinc supplementation to the pneumonia treatment regimen in children. In their clinical trial, they treated 2-23 months old Indian children with pneumonia with oral zinc and placebo during hospitalization and at the same time with antibiotic therapy, and observed that in terms of duration of tachypnea, hypoxia, eating disorders, lethargy, and length of hospitalization there is no difference between the two groups (29).

In another study, Huai et al. in 2018, in a large clinical trial, randomly treated 600 children and infants 2-5 months old with severe pneumonia with an antibiotic regimen with or without zinc. The rate of treatment failure in the two groups was the same and the time until complete recovery of symptoms was similar in the two groups. Their results were similar to those of the present study (30).

Table-2: Frequency of different clinical symptoms in the three groups in the age range of 1-3 months

Symptoms	Groups	0	1	2	3	4	5	6	7	8	9
SCR[7]	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	7(100)	7(100)	6(85.7)	6(85.7)	3(42.9)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	5(100)	5(100)	2(40)	2(40)	0(0)	0(0)	0(0)	-	-	-
	P value	-	-	0.152	0.152	0.205	-	-	-	-	-
ICR[8]	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	6(85.7)	4(57.1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	3(60)	1(20)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.364	0.293	-	-	-	-	-	-	-	-
SSR[9]	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	1(4.3)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	1	-	-	-	-	-	-	-	-	-
Cough	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	7(100)	7(100)	7(100)	7(100)	7(100)	5(100)	3(100)	3(100)	1(100)	1(100)
	AB+Zn	5(100)	5(100)	5(100)	5(100)	5(100)	5(100)	2(100)	-	-	-
	P value	-	-	-	-	-	-	-	-	-	-
Nasal Flaring	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-
Wheezing	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	3(42.9)	3(42.9)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	2(40)	2(40)	1(20)	1(20)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	1	1	0.417	0.417	-	-	-	-	-	-
Crackle	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	7(100)	7(100)	7(100)	7(100)	7(100)	4(80)	1(33.3)	1(33.3)	0(0)	0(0)
	AB+Zn	5(100)	5(100)	5(100)	5(100)	5(100)	5(100)	2(100)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	1	0.400	0.500	-	-
Diarrhea	Ab	-	-	-	-	-	-	-	-	-	-
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	1(20)	1(20)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.417	0.417	-	-	-	-	-	-	-	-

[7] Subcostal Retraction
[8] Intercostal Retraction
[9] Suprasternal Retraction

Table-3: Frequency of different clinical symptoms in the three groups in the age range of 3-12 months

Symptoms	Groups	0	1	2	3	4	5	6	7	8	9
SCR	Ab	12(100)	12(100)	4(33.3)	4(33.3)	2(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	11(100)	11(100)	4(36.4)	4(36.4)	2(18.2)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	16(100)	16(100)	5(31.2)	5(31.2)	2(12.5)	2(28.6)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	1	1	1	0.163	-	-	-	-
ICR	Ab	10(83.3)	6(50)	3(25)	1(8.3)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	8(72.7)	3(27.3)	1(9.1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	13(81.2)	5(31.2)	2(12.5)	1(6.2)	1(6.2)	1(14.3)	0(0)	0(0)	0(0)	0(0)
	P value	0.782	0.531	0.629	1	1	0.600	-	-	-	-
SSR	Ab	3(25)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	3(18.8)	1(6.7)	1(6.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.280	0.838	0.000	-	-	-	-	-	-	-
Cough	Ab	12(100)	12(100)	12(100)	12(100)	12(100)	8(100)	3(100)	1(100)	-	-
	Ab+syn	11(100)	11(100)	11(100)	11(100)	11(100)	5(100)	4(100)	2(100)	-	-
	AB+Zn	16(100)	16(100)	16(100)	16(100)	16(100)	7(100)	3(100)	1(100)	1(100)	1(100)
	P value	-	-	-	-	-	-	-	-	-	-
Nasal Flaring	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	1(6.2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-
Wheezing	Ab	5(41.7)	1(8.3)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	7(63.6)	3(27.3)	2(18.2)	1(9.1)	1(9.1)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	22(62.5)	7(43.8)	2(12.5)	1(6.2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.5	0.5	0.360	0.741	0.282	-	-	-	-	-
Crackle	Ab	11(91.7)	11(91.7)	11(91.7)	11(91.7)	11(91.7)	7(87.5)	2(66.7)	0(0)	0(0)	0(0)
	Ab+syn	11(100)	11(100)	11(100)	11(100)	11(100)	5(100)	4(100)	2(100)	0(0)	0(0)
	AB+Zn	15(100)	15(100)	15(100)	15(100)	14(100)	7(100)	2(100)	1(100)	1(100)	0(0)
	P value	0.605	0.605	0.605	0.605	0.605	1	0.556	0.500	-	-
Diarrhea	Ab	1(8.3)	1(8.3)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	1(9.1)	2(18.2)	3(27.3)	1(9.1)	1(9.1)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	2(13.3)	2(13.3)	1(6.7)	0(0)	1(6.7)	1(6.7)	0(0)	0(0)	0(0)	0(0)
	P value	1	0.847	0.123	-	0.744	0.579	-	-	-	-

Table-4: Frequency of different clinical symptoms in the three groups in the age range of 12-36 months

Symptoms	Groups	0	1	2	3	4	5	6	7	8	9
SCR	Ab	19(95)	19(95)	3(15)	3(15)	0(0)	0(0)	0(0)	-	-	-
	Ab+syn	13(100)	13(100)	3(23.1)	3(23.1)	1(7.7)	1(20)	1(50)	0(0)	0(0)	0(0)
	AB+Zn	15(100)	15(100)	4(26.7)	4(26.7)	3(20)	1(12.5)	1(25)	1(50)	0(0)	0(0)
	P value	1	1	0.669	0.669	0.117	0.260	0.667	-	-	-
ICR	Ab	11(55)	7(35)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	5(38.5)	3(23.1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	11(73.3)	15(33.3)	3(20)	2(13.3)	2(13.3)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.174	0.792	0.06	0.162	0.162	-	-	-	-	-
SSR	Ab	2(10)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	2(15.4)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	1(6.7)	1(6.7)	1(6.7)	1(6.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.849	0.583	1	0.583	-	-	-	-	-	-
Cough	Ab	20(100)	20(100)	20(100)	20(100)	20(100)	12(100)	3(100)	-	-	-
	Ab+syn	13(100)	13(100)	13(100)	13(100)	13(100)	5(100)	2(100)	1(100)	1(100)	0(000)
	AB+Zn	14(93.3)	14(93.3)	14(93.3)	14(93.3)	14(93.3)	(87.5) 7	3(75)	1(100)	-	-
	P value	0.583	0.583	0.583	0.583	0.583	0.520	1	-	-	-
Nasal Flaring	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	1(6.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-
Wheezing	Ab	8(40)	1(5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	3(23.1)	1(7.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	6(40)	5(33.3)	2(13.3)	1(6.7)	1(6.7)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.6	0.061	0.162	0.583	0.583	-	-	-	-	-
Crackle	Ab	20(100)	20(100)	20(100)	20(100)	20(100)	12(100)	3(100)	0(0)	0(0)	0(0)
	Ab+syn	13(100)	13(100)	13(100)	13(100)	13(100)	5(100)	2(100)	1(100)	1(100)	0(0)
	AB+Zn	14(93.3)	14(93.3)	14(93.3)	14(93.3)	14(93.3)	8(100)	3(75)	1(50)	1(100)	0(0)
	P value	0.583	0.583	0.583	0.583	0.583	-	1	1	-	-
Diarrhea	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	1(7.7)	1(7.7)	1(7.7)	1(7.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	2(13.3)	1(6.7)	1(6.7)	1(6.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.255	0.504	0.504	0.504	-	-	-	-	-	-

Table-5: Frequency of different clinical symptoms in the three groups in the age range of 36-72 months

Symptoms	Groups	0	1	2	3	4	5	6	7	8	9
SCR	Ab	6(100)	6(100)	1(16.7)	1(16.7)	0(0)	0(0)	-	-	-	-
	Ab+syn	8(100)	8(100)	4(50)	4(50)	1(12.5)	1(20)	1(25)	0(0)	0(0)	0(0)
	AB+Zn	5(100)	5(100)	2(40)	2(40)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	0.507	0.507	1	1	1	-	-	-
ICR	Ab	4(66.7)	3(50)	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	5(62.5)	3(37.5)	1(12.5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	2(40)	2(40)	1(20)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.713	1	1	-	-	-	-	-	-	-
SSR	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	3(37.5)	2(25)	1(12.5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.089	0.310	1	-	-	-	-	-	-	-
Cough	Ab	6(100)	6(100)	6(100)	6(100)	6(100)	3(100)	-	-	-	-
	Ab+syn	8(100)	8(100)	8(100)	8(100)	8(100)	5(100)	1(100)	1(100)	-	-
	AB+Zn	4(80)	4(80)	4(80)	4(80)	4(80)	2(100)	1(100)	-	-	-
	P value	0.263	0.263	0.263	0.263	0.263	-	-	-	-	-
Nasal Flaring	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-
Wheezing	Ab	4(66.7)	2(33.3)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	4(50)	1(12.5)	1(12.5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.88	0.434	1	-	-	-	-	-	-	-
Crackle	Ab	6(100)	6(100)	6(100)	6(100)	6(100)	3(100)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	6(75)	6(75)	6(75)	6(75)	6(75)	3(60)	3(75)	0(0)	0(0)	0(0)
	AB+Zn	5(100)	5(100)	5(100)	5(100)	5(100)	5(100)	1(100)	0(0)	0(0)	0(0)
	P value	0.310	0.310	0.310	0.310	0.310	0.667	1	-	-	-
Diarrhea	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	1(20)	1(20)	1(20)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	0.263	0.263	0.263	-	-	-	-	-	-

Table-6: Frequency of different clinical symptoms in the three groups in the age range of 72-120 months

Symptoms	Groups	0	1	2	3	4	5	6	7	8	9
SCR	Ab	7(100)	7(100)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	5(83.3)	5(83.3)	1(16.7)	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	3(75)	3(75)	1(25)	1(25)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.485	0.485	0.485	0.485	-	-	-	-	-	-
ICR	Ab	2(28.6)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	3(50)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	2(50)	1(25)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.694	1	-	-	-	-	-	-	-	-
SSR	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-
Cough	Ab	7(100)	7(100)	7(100)	7(100)	7(100)	2(100)	-	-	-	-
	Ab+syn	5(83.3)	5(83.3)	5(83.3)	5(83.3)	5(83.3)	3(75)	2(100)	2(100)	1(100)	1(100)
	AB+Zn	3(75)	3(75)	3(75)	3(75)	3(75)	1(100)	1(100)	1(100)	1(100)	1(100)
	P value	0.485	0.485	0.485	0.485	0.485	1	-	-	-	-
Nasal Flaring	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-
wheezing	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	0.588	-	-	-	-	-	-	-	-	-
Crackle	Ab	7(100)	7(100)	7(100)	7(100)	2(100)	0(0)	0(0)	0(0)	0(0)	
	Ab+syn	6(100)	6(100)	6(100)	6(100)	4(100)	2(100)	2(100)	0(0)	0(0)	
	AB+Zn	4(100)	4(100)	4(100)	4(100)	1(100)	1(100)	1(100)	1(100)	0(0)	
	P value	0.310	0.310	0.310	0.310	-	-	-	-	-	
Diarrhea	Ab	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Ab+syn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	AB+Zn	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	P value	-	-	-	-	-	-	-	-	-	-

Nonetheless, there have been studies that show the role of taking zinc with antibiotics in speeding up the treatment process and reducing the length of hospitalization in children with pneumonia. Among them, we can mention the study of Qasemzadeh et al. and Sazaval et al. (31, 32). However, this study is relatively older than the recent studies that have not reported positive results of zinc therapy in the treatment of pneumonia in children. It should be noted that one of the main underlying factors in the worsening of pneumonia in children and the failure of treatment is serum zinc deficiency (33). Therefore, it is possible that the reason for observing the effectiveness of zinc supplementation in older studies and the lack of such a finding in newer studies be the lifestyle changes and increased use of dietary supplements in children and finally the lack of background deficiency in patients.

The results of the present study on the effects of probiotic prescription in combination with antibiotic treatment of children with pneumonia showed that this treatment has no significant clinical benefit and has not prevented antibiotic-induced diarrhea.

There was no independent study on the therapeutic effect of probiotics in prescription with antibiotic regimens in children with pneumonia. Most of the attention was paid to the preventive power of these substances in ventilator-associated pneumonia prevention in severely ill children or its ability to prevent otitis. However, there is no consensus in these two cases either.

In another study in 2007, Hatakka et al. examined the effect of probiotics in the treatment of acute otitis media for 6 months. According to the results, probiotics had no effect on reducing the length of disease episodes and new episodes of the disease (34). In 2009, Rautava et al. investigated the effect of specific probiotics in reducing the risk of acute respiratory infections over 10-12 months. The results showed that new episodes of the disease were reduced (35). In 2011, Taipale et al. studied the effect of probiotics on reducing the risk of respiratory infections, including sinusitis, pneumonic bronchitis, and acute otitis media in infants over 6 to 7 months. The results indicated that new episodes of the disease decreased but no effect on the symptoms of the disease was observed (36). In 2013, Cohen et al. examined the effect of probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children. The duration of the treatment was 12 months. The results demonstrated that the use of probiotics and prebiotics had no effect on reducing the symptoms of the disease and reducing new episodes of the disease (37).

In another study by Banupriya et al. (2015), the effects of probiotics in the prevention of ventilator-associated infections in children (up to 12 years of age) were investigated in a double-blind clinical trial. The incidence of ventilator-associated pneumonia in the interventional and placebo groups was reported to be 17.1% and 48.6%, respectively ($p = 0.001$); and in the regression model, the use of probiotics was one of the most important factors in reducing the risk of ventilator-associated pneumonia, which reduced the risk by 77% (18).

In the present study, serum zinc levels were not evaluated in patients before the study and therefore the effectiveness of its use in the presence or absence of serum levels is unknown. Therefore, its potential interfering effect in the two groups is unclear. Hence, it is suggested that this issue be examined in future studies.

5- CONCLUSION

Although the beneficial effects of probiotics in modifying the microbial flora of the gastrointestinal tract has been

proven, according to the results of the present study, adding zinc or probiotics to the treatment regimen of infants and children with bacterial pneumonia is not useful and their routine prescription in combination with antibiotics do not seem to have an effect on the treatment of bacterial pneumonia.

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7- CONFLICT OF INTEREST: None.

8- AUTHOR CONTRIBUTIONS

This research was conducted in the form of a doctoral dissertation on clinical specialization in pediatrics, which was approved by the medical school of Sabzevar University of Medical Sciences. All costs of this project were provided by the Vice-Chancellor for Research of Sabzevar University of Medical Sciences. A. Keykhosravi and M. Rasti Sani designed the study, and observed its accuracy and validity. M. J. Akbarian participated in the data collection. A. Keykhosravi and M. Rasti Sani supervised the project. M. Nematshahi did datacleaning and supported the analysis of the data. S. Binesh wrote the manuscript. All authors edited and revised the final manuscript and accepted its publication.

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