



Zinc and probiotic supplementation: Effect on the frequency and duration of acute diarrhea in children under five

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ARTICLE INFO

Article history:

Received 19 March 2023

Accepted 15 June 2023

Published 30 June 2023

Keyword:

acute diarrhea
children under five, zinc supplements
probiotic supplements
frequency
duration

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DOI: 10.30604/jika.v8i2.2141
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ABSTRACT

Introduction: Diarrhea can be prevented and treated with simple and affordable interventions. The government has also implemented this strategy to prevent and control diarrhea. The World Health Organization (WHO) has recommended evidence-based, cost-effective strategies to reduce the burden of diarrheal disease. Those strategies include oral rehydration solutions (ORS), zinc supplementation, and a nutritious diet. Proper implementation of diarrhea management guidelines improves child survival. Zinc supplementation at the right dose can reduce the intensity of subsequent diarrhea. Several specific strains of probiotics, such as *Lactobacillus GG*, *L. Reuteri*, *Saccharomyces boulardii*, and *Bifidobacteria* species, have been proven to significantly play an important role in overcoming the problem of acute diarrhea in children, especially reducing the duration and severity of diarrhea. **Objective:** Examine the effect of zinc and probiotic supplementation on reducing the frequency and duration of acute diarrhea in children under five (7-59 months) in the working area of Puskesmas Tlogowungu, Pati Regency. **Materials and Methods:** This study was experimental research with a double-blind randomized controlled trial (RCT) design with a control group. The study sample was divided into three groups regarding the inclusion and exclusion criteria. **Results:** The average length of acute diarrhea in children under five before supplementation was 1.28 days (30.85 hours). After the administration of the supplement, it became 1.51 days (36.34 hours, SD ± 0.818, 95% CI = 1.23–1, 80). Based on the statistical test table, Asymp.Sig. (2-tailed) = 0.035 and 0.027 or p-value < 0.05, meaning that there was a significant effect of zinc and probiotic supplementation on a decrease in the frequency and duration of acute diarrhea in children under five, in the working area of Puskesmas Tlogowungu, Pati Regency. **Conclusion:** There is a significant effect of zinc and probiotic supplementation on a decrease in the frequency and duration of acute diarrhea in children under five in the working area of Puskesmas Tlogowungu, Pati Regency, from September to October 2022.

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INTRODUCTION

Globally, diarrheal disease is the second leading cause of death among children under five years of age. The World Health Organization (WHO) estimates that annually, 1.5 million children in this age group die from diarrheal diseases. Many studies found that the prevalence of the acute diarrheal disease varies from one country to another. About 23% of mortality in children under five years in this country caused by diarrheal disease alone.¹

The most common causes of all diarrheal disease among children under five worldwide are several bacteria, including *Vibrio cholera*, *Clostridium botulinum*, *Campylobacter jejuni*, *Escherichia coli*, *Salmonella* sp., *Staphylococcus aureus*, and *Shigella* sp. Polluted water sources, bacterial infections, malnutrition, poor personal hygiene, and poor living conditions all contributed to the onset of acute diarrheal in children under five.²

The diarrheal disease can be prevented and treated simply and cost-effectively. Improved clean water source

and sanitation, adequate nutrition, increased use of oral rehydration therapy (ORT), exclusive breastfeeding practices, optimum complementary foods intake, vaccination, and food safety awareness are recommended approaches to reduce diarrheal diseases.³

The WHO has recommended cost-effective, evidence-based strategies for reducing the burden of diarrheal disease. These strategies include the administration of oral rehydration solutions (ORS), zinc supplementation, and adequate intake of nutritious food. Moreover, the administration of antibiotics is considered unnecessary for most diarrheal cases. Proper implementation of diarrheal disease management guidelines improves child survival.⁴

Zinc tablets are micronutrients that play an important role in cell growth, act as antioxidants, form body immunity, and perform certain intestinal functions. Zinc supplementation at a 10 mg/day dose for ten days is given to infants younger than two months old. Whereas in children, zinc supplementation is given at a dose of 20 mg/day for ten days. According to the dose, zinc supplementation is intended to reduce the intensity of subsequent diarrhea.⁵

Various probiotic species that have been widely studied are *Lactobacillus rhamnosus*, *Lactobacillus GG*, *Lactobacillus acidophilus*, *Saccharomyces boulardii*, *Streptococcus thermophilus*, *Bifidobacterium*, and *Bacillus*. Probiotics are considered effective in preventing antibiotic-associated diarrhea because they can contribute to providing an ecological balance in the gut microbiota.⁶

Research Riskiyah (2017) in Malang shows that zinc supplementation is beneficial for treating diarrhea in infants, children under five, and older children because it can reduce the duration of diarrhea, stool volume, and frequency of diarrhea.⁷ Research Thomas (2017) in India showed that in children older than six months of age, zinc supplementation might shorten the average duration of diarrhea by about half a day and might reduce the number of children whose diarrhea continued to day 7.⁸ Research Oviani (2015) in Bali showed that there was no difference in stool consistency, frequency, and duration of acute diarrhea in children who received standard therapy compared to standard therapy with the addition of probiotics.⁹ In addition, research Mulyani (2016) in Yogyakarta showed that the pattern of diarrheal disease management is divided into three main types of therapy. The first is rehydration therapy and zinc supplementation, the second is rehydration therapy with both zinc and probiotic supplementation, and the third is rehydration therapy and probiotic supplementation.¹⁰ The purpose of this study was to determine the effect of zinc and probiotic supplementation in reducing the frequency and duration of acute diarrhea in children aged 7-59 months in the working area of Puskesmas Tlogowungu, Pati Regency. The benefit of the current study is to increase public knowledge about the effect of zinc and probiotic supplementation to shorten the frequency and duration of acute diarrhea in children under five. In addition, this zinc and probiotic supplementation is expected to shorten the length of hospitalization.

METHODS

Research Design And Participant Characteristics

This study was an experimental research with a double-blinded randomized controlled trial (RCT) design with a control group. The sample in this study was divided into

three groups; group I was given zinc supplements (n= 35) as a control, group II was given probiotic supplements (n= 35), and group III was given zinc and probiotic supplements (n= 35). This research was conducted in the working area of Puskesmas Tlogowungu, Pati Regency, for two months, from September to October 2022. The inclusion criteria include: 1) children who have received written consent from parents/caregivers, 2) children aged 7 to 59 months, 3) children with acute diarrhea – watery stools, with three or more times defecation frequency a day, with or without blood/mucus for seven consecutive days – and was clinically diagnosed by a physician, 4) children with mild, moderate, severe dehydration, and were outpatients or inpatients at Puskesmas Tlogowungu.

Ethical Clearance

This research was approved and obtained ethical permission from the Health Research Ethics Commission (KEPK), Faculty of Medicine, Diponegoro University (FK-UNDIP), Semarang, as stated in Ethical Clearance No.92/KEPK-RSISA/VIII/2022 dated August 31, 2022.

Sampling Procedures

The sampling technique used in this study was purposive sampling—a non-random sampling form. The technical procedures performed in this study include the following stages. First, the researchers involved health workers (midwives) of the Puskesmas as data collectors, responsible for collecting the study subject's data—children under five with acute diarrhea who have a health assessment at the Puskesmas. Beforehand, the researcher explained to the midwife for an hour to equalize perceptions about research procedures, duties, and responsibilities and explained the purpose of the questionnaire points and the intervention procedures. Next, two prospective data collectors (midwives) and researchers were assigned to distribute questionnaires, zinc supplements, and probiotics to the subjects. The researcher introduced himself to the subject, explained the research information, objectives, and procedures, and asked for the subject's willingness to participate as a study sample. The researchers selected the study samples based on the inclusion criteria to minimize confounding variables that could interfere with the study results.

Then, questionnaires were distributed from the first day of the study until a total sample of 105 children under five with acute diarrhea was met. A short questionnaire was distributed to obtain the sociodemographic characteristics of the subjects and the effect of zinc and probiotic supplementation in reducing the frequency and duration of acute diarrhea in children under five for the next seven consecutive days. Furthermore, zinc supplements were distributed from the first day of the study until 35 samples were obtained, and the effect of supplementation was observed for the next ten days. Information about the effect of zinc supplementation on reducing the frequency and duration of acute diarrhea in children under five was obtained from the mother's cellphone number. Next, probiotic supplementation was performed after or simultaneously with the zinc supplementation group until 35 samples were obtained, and the effect was observed for the next five days. Information about the effect of probiotic supplementation on reducing the frequency and duration of acute diarrhea in children under five was obtained from the mother's cellphone number. The combination of zinc and probiotic supplements was distributed after or

simultaneously with the probiotic supplementation group until 35 samples were obtained. Then, the effect was observed for the next seven days. Information about the effect of zinc and probiotic supplementation on reducing the frequency and duration of acute diarrhea in children under five was obtained from the mother's cellphone number.

All data collection activities for the control group and the intervention group (with treatment) were conducted in the working area of Puskesmas Tlogowungu, Pati Regency. The treatment group was divided into three sub-groups; 1) zinc supplementation group (with a dose of 10 mg/day for infants aged ≤ 6 months and 20 mg/day for children aged > 6 months), 2) probiotic supplementation group (with a dose of $\frac{1}{2}$ sachet x 10¹⁰ cfu/day for infants aged ≤ 6 months and one sachet x 10¹⁰ cfu/day for children aged > 6 months), and

3) zinc plus probiotic supplementation group. Data collection activity for the intervention group was conducted simultaneously after the seventh intervention day in each treatment group. Then, the data obtained from the questionnaire and the intervention results from the three treatment groups were processed and analyzed by the researchers regarding the research objectives.

Sample Size, Power, and Precision

From the sample size calculations, a minimum of 32 samples was obtained. However, to avoid missing observations (estimated dropout), the sample size was increased by 10%. Therefore, a total sample of 35 subjects was obtained for each group. In total, 105 children under five with acute diarrhea were recruited as study subjects. The difference between the three groups was considered significant at a probability value of $p < 0.05$ with a 95% confidence interval (CI) and standard deviation (\pm SD).

Measures And Covariates

The frequency of acute diarrhea in children under five was the number of defecation per day (calculated as times-per-day) since the child had diarrhea, then having an examination in the Puskesmas/hospital as outpatient/inpatient, and until after the child was being treated/recovered. The measurement result of watery stool per day; 3-5 times (rare) and 6-8 times (often), with an interval scale. The duration of acute diarrhea in children under five was the length of time (calculated as hour(s)-per day in a week) since the child had diarrhea, then having examination in the Puskesmas/hospital as outpatient/inpatient, and until the diarrhea was stopped/recovered. The measurement results on the duration of being recovered from diarrhea include 1-3 days (short) and 4-7 days (long). Probiotic supplementation was the administration of a supplement in the form of a white powder containing 10⁹ cfu of *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Streptococcus thermophilus* bacteria strains for five days at a dose of $\frac{1}{2}$ sachet x 10¹⁰ cfu per day (≤ 6 months) and one sachet x 10¹⁰ cfu per day (> 6 months), on a nominal scale. Zinc and probiotic supplementation were the administration of oral zinc at a standard dose (10 mg or 20 mg per day) in children under and over the age of 6 months, combined with the probiotic preparations for ten days administration at a dose of 10mg/day + $\frac{1}{2}$ sachet x 10¹⁰ cfu per day (≤ 6 months) and 20 mg/day + 1 sachet x 10¹⁰ cfu per day (> 6 months). Data on children under five with acute diarrhea were obtained from direct interviews using a questionnaire to mothers who had

their children examined at Puskesmas Tlogowungu or via home visits.

Data Analysis

The Mann-Whitney U-test was used as an alternative to the t-test and z-test in the intervention group to observe the differences between the two groups of independent variables whose data were not normally distributed. Moreover, the Wilcoxon test was used to examine two data samples from the dependent variable and aims to test whether the two have an association. The Wilcoxon test was used as an alternative to the paired t-test in the control group. Whereas for data on three or more groups of unrelated independent variables, a non-parametric test in the form of the Kruskal Wallis test was used as an alternative to the ANOVA test. The difference between the three groups was considered significant at a probability value of $p < 0.05$ with a 95% confidence interval (CI) and standard deviation (\pm SD).

Univariate analysis was performed to describe data on each variable, including independent variables (zinc supplementation, probiotic supplementation, and zinc-probiotic supplementation), dependent variables (frequency and duration of acute diarrhea in children under five), and confounding variables (sociodemographic characteristics), in children under five in the working area of Puskesmas Tlogowungu, Pati Regency. Next, the bivariate analysis was performed to observe the association of each data variable, including independent variables (zinc supplementation, probiotic supplementation, and zinc-probiotic supplementation), dependent variables (frequency and duration of acute diarrhea in children under five), and confounding variables (sociodemographic characteristics), in children under five in the working area of Puskesmas Tlogowungu, Pati Regency. Finally, multivariate analysis was performed by simultaneously associating the independent variables with one dependent variable. This study also used simple and multiple regression tests to determine which interventions had the most effect on reducing the frequency and duration of acute diarrhea in children under five.

RESULTS AND DISCUSSION

Table 1 shows the distribution of sociodemographic data on children under five with acute diarrhea based on each intervention group, including the child's age, child's sex, and child's nutritional status. The mean age of this study subjects was 29.80 months, with 12 children (11.43%) aged 7-12 months and the majority (88.57%) of the subjects aged 13-59 months. According to the child's sex, 62 male children (59.05%) experienced more acute diarrhea than females (n= 43, 40.95%). In addition, based on the nutritional status variable, most subjects had a normal nutritional status (n= 74, 70.48%), and 31 subjects (29.25%) were undernourished. Overall, most of the subjects had acute diarrhea with mild dehydration.

The effect of probiotic supplementation to reduce the frequency and duration of acute diarrhea in children under five

Table 2 shows the mean value of the frequency of acute diarrhea in children under five before probiotic supplementation (4.82 times/day) and after supplementation

(0.94 times/day) with SD ± 0.906 and 95% CI = 0.63–1.25. While the mean value of the duration of acute diarrhea in children under five before supplementation was 1.42 days

(34.28 hours), and after supplementation became 1.91 days (45.94 hours) with SD ± 0.853 and 95% CI = 1.62–2.21 on the SPSS descriptive table.

Table 1. Distribution of sociodemographic data on children under five with acute diarrhea

Characteristics	Control		Probiotics		Zinc-Probiotics	
	n=35	(%)	n=35	(%)	n=35	(%)
Child's age						
Infant (<1 year)	3	(8.57)	7	(20.00)	2	(5.71)
Toddler (1-5 years)	32	(91.43)	28	(80.00)	33	(94.29)
Child's sex						
Male	19	(54.29)	21	(60.00)	22	(62.86)
Female	16	(45.71)	14	(40.00)	13	(37.14)
Child's nutritional status						
Normal	10	(28.57)	13	(37.14)	7	(20.00)
Undernutrition	25	(71.43)	22	(62.86)	28	(80.00)

Table 2. The effect of probiotic supplementation to reduce the frequency and duration of acute diarrhea in children under five

Dependent variable	Probiotic		Sig.	SD	95% CI
	Before	After			
The frequency of acute diarrhea	4.82 times	0.94 times	0.035	0.906	0.63 – 1.25
The duration of acute diarrhea	1.42 days	1.91 days	0.027	0.853	1.62 – 2.21

Analyzed by the Mann-Whitney test

Based on statistical tests, Asymp. Sig. (2-tailed) = 0.035 and 0.027 or *p*-value

<0.05 was obtained. This means that there was a significant effect of probiotic supplementation in reducing the frequency and duration of acute diarrheal disease in children under five in the working area of Puskesmas Tlogowungu, Pati Regency, from September to October 2022.

After researching children under five who experienced acute diarrhea by administering probiotic supplements using the double-blind RCT method at Puskesmas Tlogowungu, Pati Regency, the results showed an effect of probiotic supplementation on the frequency and duration of acute diarrhea in these under-five children.

Probiotic supplementation has an effect on reducing the frequency of acute diarrhea in children under five. The effect of probiotic supplementation could reduce the frequency of acute diarrhea in children under five with Sig. 0.035 (*p* <0.05). This finding indicates a significant decrease in the frequency of acute diarrhea cases in children under five. Ciptaningtyas (2020) found that probiotic supplementation had a positive effect on the frequency of diarrhea in children under five. This positive effect indicates a decrease in the frequency of children under five with acute diarrhea cases, potentially speeding the recovery.¹¹ Novini (2021) reported that the mechanism of probiotics might shorten the course and reduce the frequency of diarrhea in children under five. The decrease in diarrhea in children under five, which can ultimately reduce the frequency of diarrhea, indicates a decrease in the frequency in children under five with cases of acute diarrhea so that they experience recovery.¹²

Probiotic supplementation has an effect on reducing the duration of acute diarrhea in children under five. Giving probiotic supplements can reduce the duration of acute diarrhea in children under five with Sig 0.027 (*p* <0.05), which shows a decrease in the duration of children under five with cases of acute diarrhea so that they experience recovery. Huang (2021) found that giving probiotic supplements for treating acute diarrhea in children shortens the duration of diarrhea and the length of hospital stay. In

short, the duration of acute diarrhea and hospital stay in children under five decreases, so they experience recovery.¹³ Mosaddek (2022) reported that the use of probiotics in the treatment of acute diarrhea in children appears to be effective, safe, and was associated with a shorter and faster duration of diarrhea. The shorter duration of diarrhea indicates a decrease in the duration of acute diarrhea experienced by children under five so that they experience recovery.¹⁴

Andrea (2018) found that probiotics were assumed to positively affect the gut microflora, stool consistency, and defecation frequency. However, not a few of the existing studies show contradictory results. An open trial demonstrated the effect of *Bifidobacterium breve* on increasing the defecation frequency in children with functional constipation. In addition, *Bifidobacterium breve* has positively affected stool consistency, reduced fecal incontinence episodes, and reduced abdominal pain. In another open trial, the supplementation of a combination of probiotics consisting of *B. bifidum*, *B. infantis*, *B. longum*, *L. casei*, *L. plantarum*, and *L. rhamnosus* improved constipation symptoms. Probiotic *L. casei rhamnosus* (Lcr35) was also reported to have an effective result in the management of children with chronic constipation. Patients receiving Lcr35 had a higher defecation frequency and softer stools than the placebo group. Similarly, *L. reuteri* (DSM 17938) also positively affected peristaltic movement in infants with chronic constipation, although there was no improvement in stool consistency and crying episodes. Moreover, yogurt supplemented with *B. longum* has positively affected defecation frequency. However, probiotic supplementation has also raised a safety concern, especially for the *Lactobacilli* dan *Bifidobacterium* strain. Every probiotic carries risks, particularly in the context of host susceptibility. Nonetheless, probiotics are "considered safe," and side effects are barely reported on an outpatient basis. Invasive infections in infants and children are very rare. Clinically, there may be a transfer of antibiotic resistance plasmids. Long-term use of probiotics with strict antibiotic selection

can cause antibiotic resistance, and resistance genes can be transferred to other bacteria. The potential for transferring antibiotic resistance appears to be low with currently available probiotic products. The translocation of bacteria from the gastrointestinal tract into systemic circulation has never been reported. Probiotic supplementation must be performed with caution, especially in children with conditions that have the potential to disrupt the integrity of the gastrointestinal mucosa. The bacterial strain should be considered in assessing safety. Probiotic supplementation must consider the benefits obtained and the risk of invasive infection.¹⁵

The effect of zinc-probiotic supplementation to reduce the frequency and duration of acute diarrhea in children under five

Table 3 shows the mean frequency of acute diarrhea in children under five before zinc probiotic supplementation was 4.94 times/day, and after the supplementation was 0.62 times/day [SD ± 1.140 and 95% CI = 0.24–1.02]. Meanwhile, the mean duration of acute diarrhea in children under five before supplementation was 1.28 days (30.85 hours) and after supplementation became 1.51 days (36.34 hours) with SD ± 0.818 and 95% CI = 1.23–1.80 in the SPSS descriptive table.

Table 3.
The effect of zinc-probiotic supplementation to reduce the frequency and duration of acute diarrhea in children under five

Dependent variable	Zinc-Probiotic		Sig.	SD	95% CI
	Before	After			
The frequency of acute diarrhea	4.94 times	0,62 times	0.035	1.140	0.24 – 1.02
The duration of acute diarrhea	1.28 days	1.51 days	0.027	0.818	1.23 – 1.80

Analyzed with the Mann-Whitney test

Based on the statistical test, Asymp. Sig. (2-tailed)= 0.035 and 0.027 or *p*-value < 0.05 was obtained. This means that there was a significant effect in zinc-probiotic supplementation with the lower frequency and duration of acute diarrhea in children under five at the working area of Puskesmas Tlogowungu, Pati Regency, from September to October 2022.

The provision of zinc and probiotic supplements reduce the frequency of acute diarrhea in children under five. The effect of probiotic supplementation can reduce the frequency of acute diarrhea in children under five with Sig.0.035 (*p* < 0.05), which indicates the recovery rate. Rahmayani (2014) found that the frequency of diarrhea could be shortened through zinc and probiotics supplementation. The shortened defecation frequency shows a decrease in the frequency of defecation in children under five with acute diarrhea cases so that they experience recovery.¹⁶

Zinc and probiotic supplementation have an effect on reducing the duration of acute diarrhea in children under five. Nurmainah (2017) reported that giving a combination of zinc and probiotics to pediatric patients with acute diarrhea cases has an impact on the length of hospital stay. The study concluded that the average length of hospital stay for patients with mild diarrhea without infection was 2.42 days, while in patients with mild diarrhea plus infection was 4.26 days. The short length of hospital stays and no infection showed to improve the recovery rate.¹⁷ Mahen (2017) found that the combination of zinc and probiotic therapy was more effective than probiotics alone in reducing the severity of acute diarrhea and vomiting in children. It was found that low-socioeconomic status is a risk factor for diarrhea. The reduced severity of acute diarrhea indicates a recovery rate.¹⁸

Latif (2015) found that zinc's mechanism of action in reducing diarrhea duration was by accelerating the regeneration process of intestinal epithelial tissue. So, the new cells that will repair damaged epithelial layers will be formed, inducing water and electrolyte absorption in the intestine and increasing the immune response, leading to cleansing pathogens. A similar mechanism is also found in probiotics, with the production of bacteriocins or antimicrobial substances against intestinal pathogens, competing to inhibit the binding of pathogens with the intestinal mucosa and stimulating the immune system.

Consequently, the toddler's immunity is increased. Through this mechanism, the combination of zinc and probiotics supplementation in this study is expected to have a synergistic effect in reducing the duration of acute diarrhea. The administration of zinc and probiotic supplementation together provided longer protection against recurrent diarrhea, although there was no significant difference.¹⁹ Lolopayung (2014) reported that probiotic bacteria can help the nutrient absorption process and prevent disturbances in water absorption, which will affect the improvement of stool consistency. The mechanism is similar to zinc, which can improve or increase the absorption of water and electrolytes by reducing the water content in the intestinal lumen, which improves stool consistency. Improvement in stool consistency will reduce the defecation frequency and shorten the duration of diarrhea in children.²⁰

LIMITATIONS OF THE STUDY

This study had several limitations, including not measuring stool volume so that differences in the severity of diarrhea could not be assessed. The effect of nutritional status on decreasing the duration of acute diarrhea in each group could not be analyzed because the malnutrition status in each group was too small to be compared. Post-supplementation serum zinc levels were not measured, so the effect of supplementation in reducing the incidence of post-diarrheal zinc deficiency was not known.

CONCLUSIONS AND SUGGESTIONS

There is an effect of probiotic supplementation on reducing the frequency of acute diarrhea in children under five. There is an effect of probiotic supplementation on reducing the duration of acute diarrhea in children under five. There is an effect of zinc and probiotic supplementation on reducing the frequency of acute diarrhea in children under five. There is an effect of zinc and probiotic supplementation on reducing the duration of acute diarrhea

in children under five. It is hoped that future researchers can continue the research on the incidence of diarrhea related to other environmental health aspects.

Acknowledgment

The author would like to thank the health workers in the working area of the Tlogowungu Health Center, Pati Regency, who has provided direction, time, patience, and guidance in our research. Also, all parties who have helped write this thesis and provided support and encouragement in the writing process for supporting HC in obtaining his M.Gz degree.

Funding

HC is supported by funding from my own parents

Availability of Data and Materials (ADM)

The data of the current study belong to the Jurnal Aisyah and are restricted to be used in this study. Therefore, it is not available to access the data. Nevertheless, the data are accessible from the authors on the request and with approval by Jurnal Aisyah.

Authors' Contributions

HC was the principal investigator. HC dan AP designed the research. HC dan LK managed and retrieved the data. HC contributed to data analysis and interpretation of data. HC, AS, KT wrote the manuscript. All authors participated in critical revision of the manuscript for important intellectual content, and have read and approved the final manuscript.

Conflict of Interest

This research does not include any conflict of interest.

REFERENCES

- Fenta, A., Alemu, K., & Angaw, D. A. (2020). Prevalence and associated factors of acute diarrhea among under-five children in Kamashi district, western Ethiopia: community-based study. *BMC pediatrics*, 20, 1-7.
- Sanyaolu, A., Okorie, C., Marinkovic, A., Jaferi, U., Prakash, S., Jan, A., & Mangat, J. (2020). Global epidemiology and management of acute diarrhea in children from developing countries. *Ann Pediatr Child Health*, 8(8), 1205.
- Delelegn, M. W., Endalamaw, A., & Belay, G. M. (2020). Determinants of Acute Diarrhea Among Children Under-Five in Northeast Ethiopia: Unmatched Case- Control Study. *Pediatric Health, Medicine and Therapeutics*, 323-333.
- Behera, P., Bhatia, V., Sahu, D. P., Sahoo, D. P., Kamble Sr, R., Panda, P., ... & Singh, A. (2021). Adherence of doctors to standard diarrhoeal management guideline during treatment of under-five diarrhoeal episodes: a study from Eastern India. *Cureus*, 13(2).
- Widayati, P., Rahardjo, S. S., & Widyaningsih, V. (2019). Meta-Analysis on the Effect of Zinc on Reducing Diarrhea Episode in Toddlers. *Indonesian Journal of Medicine*, 4(2), 183-191.
- Hadiyanto, M. L., & Wahyudi, S. (2022). Probiotik sebagai Pencegahan Diare terkait Antibiotik pada Anak. *Cermin Dunia Kedokteran*, 49(4), 219-222.
- Riskiyah, R. (2017). Peranan zinc pada penanganan kasus penyakit diare yang dialami bayi maupun balita. *Journal of Islamic Medicine*, 1(1), 22-29.
- Thomas, T. A. (2017). Zinc supplementation in diarrhea: summary of Cochrane database review. *Current Medical Issues*, 15(2), 142.
- Oviani, G. A., Swastini, D. A., & Nesa, N. N. M. (2015). Suplementasi probiotik terhadap konsistensi feses, frekuensi dan durasi diare akut pada anak di RSUP Sanglah. *Jurnal Farmasi Udayana*, 4(1), 279861.
- Mulyani, S., Perwitasari, D. A., & Umam, N. (2016). Efektifitas pemberian probiotik terhadap durasi diare anak di Rumah Sakit PKU Muhammadiyah Bantul Yogyakarta. *Pharmaciana*, 8(1).
- Ciptaningtyas, W. A. D., Murti, B., & Rahardjo, S. S. (2020). Meta-Analysis: Effect of Probiotics on the Frequency and Duration of Diarrhea in Children Under Five. *Indonesian Journal of Medicine*, 5(04), 321-330.
- Novini, Khairunnisa, P., Hanifa, D. N. C. (2021). Literature Review: Efektivitas Kombinasi Zink Dan Probiotik Pada Pengobatan Diare. Prosiding Seminar Nasional Farmasi - UMKT "Up to Date Covid-19: Vaksin dan Pemanfaatan Herbal Indonesia sebagai Upaya Pencegahan Penularan Covid-19" Jun 06. 86-98.
- Huang, R., Xing, H. Y., Liu, H. J., Chen, Z. F., & Tang, B. B. (2021). Efficacy of probiotics in the treatment of acute diarrhea in children: a systematic review and meta- analysis of clinical trials. *Translational Pediatrics*, 10(12), 3248.
- Mosaddek, A. S. M. (2022). Effect of Probiotics in the Treatment of Acute Watery Diarrhoea in Children Admitted to a Tertiary Care Hospital in Bangladesh: A Non- Randomized Prospective Clinical Trial. *International Journal of Collaborative Research on Internal Medicine & Public Health*, 14(2), 1-7.
- Andrea, V., Hegar, B., & Dradjat, R. S. U. D. D. (2018). Probiotik Pada Gangguan Saluran Cerna Fungsional. *Sari Pediatri*, 20(3), 185-9.
- Rahmayani, R., Salwan, H., Bakri, A., & Husin, S. (2014). Efek Pemberian Kombinasi Zinc dan Probiotik Terhadap Lama dan Frekuensi Diare Pada Penderita Diare Akut. *Majalah Kedokteran Sriwijaya*, 46(3), 181-185.
- Nurmainah, N., Susanti, R., & Nansy, E. (2016). Gambaran Biaya dan Lama Rawat Inap Pada Pasien Diare Akut Anak Yang Menggunakan Kombinasi Suplemen Zinc- Probiotik. *Jurnal Farmasi Indonesia*, 13(2), 150-158.
- Mahen, M., Rizka, A. (2017). The Efficacy of Probiotics in Adults with Acute Infectious Diarrhea. Departement of Internal Medicine FM Universitas Indonesia. 5(1).
- Latif, H. A. (2014). Terapi suplementasi zink dan probiotik pada pasien diare. *Jurnal Agromed Unila*, 2(4), 440-445.
- Lolopayung, M., Mukaddas, A., & Faustine, I. (2014). Evaluasi penggunaan kombinasi zink dan probiotik pada penanganan pasien diare anak di instalasi rawat inap RSUD Undata Palu tahun 2013. *Natural Science: Journal of Science and Technology*, 3(1).