

The effect of zinc and probiotics supplements in children under 5 years old with diarrhea

Qhifani Zhaqila, Sugeng Ruspandi, Chairun Wiedyaningsih*

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia

<https://doi.org/10.22146/ijpther.10289>

ABSTRACT

Submitted: 27-10-2023
Accepted : 17-04-2024

Keywords:

diarrhea;
zinc;
probiotics;
children;
under the 5 years old

The 2020 Indonesian Health Profile states that diarrhea is an endemic disease that has the potential to cause extraordinary events. Diarrhea is still one of the contributors to death in Indonesia, especially in children under 5 years old. This study aimed to evaluate the use of zinc and probiotic supplementation on the length of stay (LoS) of patients under 5 years old with diarrhea. It was an observational study using medical records of patients under 5 years old with diarrhea at the Academic Hospital, UGM Yogyakarta in the period of 2021 to 2022. Patient characteristics, including use and medications such as zinc supplementation and probiotics, as well as clinical outcomes including LoS were obtained from 100 medical records. Data were analyzed using chi square from Microsoft Excel 365 & Statistical Program for Social Science (SPSS) with a 95% confidence level ($p < 0.05$). The majority of patients were male (61%) with age range 12-23 mo (47%), 3-4 times frequency of diarrhea (69%), dehydration mild-moderate (89%), and acute diarrhea (96%). The treatment of diarrhea was antidiarrheal (44.81%), fluid rehydration (32.55%), and antibiotics (22.64%). Most patients left the hospital in an improved condition and were allowed to go home (92%). There is a significant relationship between the use of zinc, probiotics, and a combination of zinc and probiotics on LoS.

ABSTRAK

Profil Kesehatan Indonesia tahun 2020 menunjukkan diare merupakan penyakit endemik yang berpotensi menimbulkan kejadian luar biasa. Diare masih menjadi salah satu penyumbang kematian di Indonesia, khususnya pada anak di bawah 5 tahun. Penelitian ini bertujuan untuk mengevaluasi penggunaan suplemen zinc dan probiotik terhadap lama tinggal (*length of stay/LoS*) pasien dibawah 5 tahun yang menderita diare. Penelitian ini merupakan penelitian observasional dengan menggunakan rekam medis pasien usia dibawah 5 tahun yang menderita diare di Rumah Sakit Akademik UGM Yogyakarta periode tahun 2021 hingga 2022. Karakteristik pasien, termasuk penggunaan dan pengobatan seperti suplementasi zinc dan probiotik, serta luaran klinis, termasuk LoS diperoleh dari 100 rekam medis. Data dianalisis menggunakan chi square dari Microsoft Excel 365 & Statistical Program for Social Science (SPSS) dengan tingkat kepercayaan 95% ($p < 0.05$). Mayoritas penderita berjenis kelamin laki-laki (61%) dengan rentang usia 12-23 bulan (47%), frekuensi diare 3-4 kali (69%), dehidrasi ringan-sedang (89%), dan diare akut (96%). Pengobatan diare yang dilakukan adalah antidiare (44,81%), rehidrasi cairan (32,55%), dan antibiotik (22,64%). Sebagian besar pasien meninggalkan rumah sakit dalam kondisi membaik dan diperbolehkan pulang (92%). Terdapat hubungan yang bermakna antara penggunaan zinc, probiotik, dan kombinasi zinc dan probiotik terhadap LoS.

INTRODUCTION

Diarrhea is still a health problem in developing countries, including Indonesia. Globally, diarrhea is one of

the leading causes of high mortality and morbidity rates in children under 5 years old. Around 1.7 billion cases of children experiences diarrhea annually, and 525,000 death due to diarrhea

*corresponding author: chairun_wied@ugm.ac.id

worldwide.¹ Most the deaths are caused by severe dehydration. In severe diarrhea, children will experience defecation in liquid form with or without mucus and blood several times a day, often accompanied by vomiting, fever, and even seizures. Therefore, the body will lose a lot of water and salt, which can result in dehydration, acidosis, and hypoglycemia, and often ends in shock and death.²

The 2020 Indonesian Health Profile reported that diarrhea is an endemic disease that can potentially cause extraordinary events. It is still one of the contributors to the death rate in Indonesia, especially in children under 5 years old.³ In 2020, the most common cause of death among children aged 12 to 59 mo in Indonesia was diarrhea, with a percentage of 4.55%.³ Data from the Yogyakarta Special Region Health Profile in 2020 demonstrated that diarrhea is still a serious event. In Yogyakarta, diarrhea sufferers are relatively high, with the number of cases being 46,399 or 46.8% of patients, including 29.2% of patients under 5 years old.⁴ In 2020 in Yogyakarta, diarrhea was ranked 6th out of the top 10 new cases of the disease in hospital inpatient installations with 3,769 patients.³

The main modality for the treatment of diarrhea include zinc supplementation which can reduce the duration of diarrheal episodes by 25% and is associated with a 30% reduction in stool volume.⁵ The Indonesian Ministry of Health has developed guideline to treat diarrhea in children, which includes providing zinc tablets for 10 consecutive days.⁶ The recommendation for the use of zinc is based on strong biological and epidemiological evidence showing that administering zinc can significantly reduce the duration, stool volume and frequency of diarrhea. Zinc therapy for children's diarrhea plays a role in restoring the body's fluid and electrolyte balance during

dehydration and providing therapy with oral rehydration solution (ORS).⁷ Another treatment for diarrhea therapy is usage of prebiotic as active treatment of gastroenteritis in addition to rehydration.⁸ Certain probiotics have demonstrated efficacy and widely used to prevent and treat medical conditions involving the digestive tract in children.⁹ In the treatment of acute diarrhea in children, the addition of probiotics can shorten the duration of diarrhea, increase treatment efficacy after 2 d of treatment, and shorten the length of hospital stay.¹⁰ The high number of cases of diarrhea sufferers in Yogyakarta and the global status of diarrhea as a contributor to mortality in children under 5 years old make it necessary to evaluate the use of zinc and probiotics supplementation in children diagnosed with diarrhea. It will be useful as zinc and probiotic supplementation usage information in children under 5 years old with diarrhea.

MATERIAL AND METHODS

Research design

It was an observational study to evaluate the treatment of patients under 5 years old with diarrhea and the relationship between treatment and clinical outcomes after receiving zinc and probiotic supplementation from 2021 to 2022. The study was conducted at the Academic Hospital, Universitas Gadjah Mada (UGM), Yogyakarta.

Experimental

The inclusion and exclusion criteria were patients with diarrhea, age between 12 to 59 mo calculated from the first day the hospitalized patient enters the inpatient ward until the patient was discharged from the hospital; received zinc treatment, probiotics or a combination of both. The

exclusion criteria were patients with comorbidities; incomplete electronic and manual medical records. Sampling was carried out by purposive sampling, and the minimum number of samples taken was calculated using the Lemeshow formula.¹¹ The sample size was based on the Lemeshow formula: if the population is known to be 297 patients, then if the degree of confidence is 95% (1.96); $p = \text{maximum estimate} = 50\% = 0.5$; $\text{sampling error} = 10\%$, therefore the minimum number of samples required in this research was 73.¹¹

Data analysis

Data was presented in the form of tables and percentages, as well as narratives. The data collected was then analyzed using univariate analysis to describe the usage of zinc and probiotic supplementation and clinical outcomes. Further bivariate analysis was also carried out to evaluate the relationship between zinc & probiotics supplementation and average length of stay (LoS). The chi-square cross-tabulation test was used to determine whether there is a relationship between the use of zinc supplementation, probiotics, or a combination of both on the average LoS. A p value <0.05 was considered significant.

RESULTS

Characteristics of diarrhea patients

The characteristics of diarrhea children under 5 years old inpatients of the Academic Hospital, UGM, Yogyakarta for 2021 to 2022 are presented in TABLE 1.

Grouping patients based on age aims to determine in what age range diarrhea most frequently occurred in inpatients in hospitals from 2021 to 2022. This study was categorized into four age

groups, namely 12-23, 24-35, 36-47, and 48-59 mo. The most frequent occurrence of diarrhea in a day in patients was 3-5 times (69%), followed by 6-8 times (17%), 9-11 times (9%), and ≥ 12 times (5%). The degree of dehydration in this study was categorized into 3, namely dehydration, mild-moderate dehydration, and severe dehydration, where mild-moderate dehydration is the most common dehydration. TABLE 1 shows that 89% of patients under 5 years old at the Academic Hospital, UGM Yogyakarta experienced mild-moderate dehydration, and 96% of cases experienced acute diarrhea.

TABLE 2 shows an overview of the use of drugs specifically to treat diarrhea. The most widely used drug to treat diarrhea was Lacto-B®, administered orally. Rehydration fluids were also used to treat diarrhea; some were given orally or intravenously. The most widely used parenteral rehydration fluid is Asering® or ringer acetate. Several antibiotics were also used to treat diarrhea cases (23.19%). TABLE 2 shows that cefixime was widely used orally as an antibiotic for diarrhea treatment. The antibiotic cefixime is given in the form of syrup and pulveres by oral administration. Apart from being given the primary medicine to treat diarrhea, several other medicines were also given to the patients, depending on the condition of the disease. Apart from the main medicine for treating diarrhea, some patients also given vitamins, antiallergics, etc. Paracetamol injection was the other most widely used drug which was given to 100 patients suffering from diarrhea at the hospital where the research was conducted (TABLE 3).

The clinical outcomes of diarrhea patients received treatment were observed from the patient's discharge status, and the average LoS is presented in TABLE 4.

TABLE 1. Characteristics of children with diarrhea under 5 years old inpatients at the Academic Hospital, UGM, Yogyakarta

| Characteristics | Number of patients (n) | Percentage (%) |
|------------------------------|------------------------|----------------|
| Age (mo) | | |
| • 12 - 23 | 47 | 47.00 |
| • 24 - 35 | 26 | 26.00 |
| • 36 - 47 | 21 | 21.00 |
| • 48 - 59 | 6 | 6.00 |
| Gender | | |
| • Male | 61 | 61.00 |
| • Female | 39 | 39.00 |
| Frequency of diarrhea (time) | | |
| • 3-5 | 69 | 69.00 |
| • 6-8 | 17 | 17.00 |
| • 9-11 | 9 | 9.00 |
| • ≥ 12 | 5 | 5.00 |
| Degree of dehydration | | |
| • No dehydration | 8 | 8.00 |
| • Mild-moderate dehydration | 89 | 89.00 |
| • Severe dehydration | 3 | 3.00 |
| Type of diarrhea | | |
| • Acute diarrhea | 96 | 96.00 |
| • Persistent diarrhea | 0 | 0.00 |
| • Dysentery | 4 | 4.00 |
| Total | 100 | 100 |

TABLE 2. The primary medicine use for treatment of diarrhea

| Class of therapy/Drug | Dosage form | Administration | Number of items per drug (n) | Total | (%) | | |
|--------------------------|------------------|--------------------|------------------------------|------------|------------|----|-------|
| Antidiarrhea | | | | | | | |
| • Zinc | Syrup | | 67 | 190 | 44.50 | | |
| • Lacto-B® | | Oral | 93 | | | | |
| • Sequest® | Pulvis | | 29 | | | | |
| • Smecta® | | | 1 | | | | |
| Rehydration fluid | | | | | | | |
| • Oralit® | Pulvis | Oral | 3 | 138 | 32.32 | | |
| • Asering® | | | 63 | | | | |
| • RD 5% | | | 22 | | | | |
| • KA-EN 3A (tridex 27A) | | | 33 | | | | |
| • KA-EN 3B (tridex 27B) | | | 5 | | | | |
| • D5 ½ | | | 5 | | | | |
| • D5 ¼ | | | 3 | | | | |
| • D5 | | | 1 | | | | |
| • NaCl 0.9% | Infuse | Intravenous | 2 | | | | |
| • Ringer laktat | | | 1 | | | | |
| Antibiotic | | | | | | | |
| • Cefixime | Syrup & pulveres | Oral | 30 | | | 99 | 23.19 |
| • Cefotaxime | | | 7 | | | | |
| • Ceftriakson | | | 16 | | | | |
| • Gentamisin | | | 3 | | | | |
| • Viccillin | Injection | Intravenous | 1 | | | | |
| • Ampicillin | | | 9 | | | | |
| • Cotrimoxazole | Syrup | Oral | 5 | | | | |
| • Amoxysilin | | | 1 | | | | |
| • Metronidazole | Syrup & pulveres | Oral & intravenous | 22 | | | | |
| • Azitromisin | | | 2 | | | | |
| • Biothiol® | Syrup | Oral | 1 | | | | |
| • Clabat forte® | | | 2 | | | | |
| Total | | | 427 | 427 | 100 | | |

TABLE 3. The use of additional medications for the treatment of diarrhea

| Drug | Dosage form | Administration | Number of item (n) |
|--------------------------|-------------|----------------|--------------------|
| Constantia® | | | 6 |
| Ferro-k® | Drop | | 2 |
| Zamel® | | 1 | |
| Nystatin® | | 4 | |
| D-vit® | | 3 | |
| Curvit® | | 1 | |
| Paracetamol | Syrup | | 2 |
| Cetirizine | | 9 | |
| Sucralfate | | Oral | 2 |
| Isprinol® | | | 1 |
| Vitamin B | | | 1 |
| Vitamin B1 | | | 1 |
| Vitamin C | | | 1 |
| Folic acid | | Pulveres | 1 |
| Diazepam | | | 15 |
| Cetirizine HCl | | | 1 |
| Chlorpheniramine maleate | 1 | | |
| Phenobarbital | 1 | | |
| Diazepam | | 6 | |
| Methylprednisolone | Injection | | 8 |
| Ondansetron | | Intravenous | 54 |
| Ranitidine | | | 2 |
| Paracetamol | Infuse | | 69 |
| Bepanthen® | Unguentum | | 9 |
| Noroid® | Lotion | | 1 |
| Mometason® | | Topical | 1 |
| Fuladic® | Cream | | 1 |
| Desolex 0.05%® | | | 2 |
| Total | | | 206 |

Note: Constantia® (nystatin); Ferro-k® (zinc); Zamel® (multi vitamin + mineral); Curvit® (multivitamin + curcumin); Isprinol® (methisoprinol); Bepanthen® (pro vitamin B5/dexpanthenol); Noroid® (moisturising cream); Mometason® (mometason); Fuladic® (fusidic acid); Desolex 0.05%® (desonide)

TABLE 4. Clinical outcome

| Category | Number of patients (n) | Degree of dehydration | | | (%) | LoS (d) |
|---------------------------|------------------------|-----------------------|---------------|--------|-----|---------|
| | | No- dehydration | Mild-Moderate | Severe | | |
| Patient improves* | 92 | 8 | 81 | 3 | 92 | 3.74 |
| Patient recovers* | 7 | 0 | 7 | 0 | 7 | 4.71 |
| Patient has not recovered | 1 | 0 | 1 | 0 | 1 | 1.00 |
| Patient died | 0 | 0 | 0 | 0 | 0 | 0.00 |
| Total | 100 | | 100 | | 100 | 2.36 |

Note: *goes home

The classification of discharge status categories was based on categories that were in the patient's medical record, which were divided into four groups, namely patients who improved and were allowed to go home, patients who recovered and were allowed to go home; the patient has not recovered but is going home own request; and the patient dies.

The relationship between the use of zinc supplements or probiotics and the average LoS is presented in TABLE 5. The study shows a significant relationship between the use of zinc, probiotics, or a combination of zinc and probiotics on

the average LoS of inpatients under five years old diagnosed with diarrhea in the Academic Hospital, UGM Yogyakarta ($p < 0.05$). TABLE 5 shows an overview of the use of antibiotics on average LoS, which is divided into 3 categories: administration without antibiotics, single antibiotics, and combination antibiotics. Based on TABLE 6, there are variations in LoS results related to the use of antibiotics in diarrhea patients who received supplements with either zinc, probiotics, or a combination of both.

TABLE 5. Relationship between the use of zinc and probiotics supplementation against the average LoS of diarrhea patients

| Therapy | Number of patients (n) | LoS (d) | p |
|-----------------------------------|------------------------|---------|-------|
| Therapy with zinc supplement | 7 | 3.86 | |
| Therapy with probiotic supplement | 29 | 3.17 | 0.000 |
| Therapy with zinc and probiotic | 64 | 3.98 | |
| Total | 100 | 3.67 | |

TABLE 6. Description of antibiotic use on average LoS

| Drug | Without antibiotic | | Single antibiotic | | Antibiotic combination | | LoS (d) |
|------------------|--------------------|---------|-------------------|---------|------------------------|---------|---------|
| | Patients (n) | LoS (d) | Patients (n) | LoS (d) | Patients (n) | LoS (d) | |
| Zinc | 0 | 0.00 | 5 | 3.40 | 2 | 5.00 | 3.86 |
| Probiotic | 1 | 2.00 | 21 | 2.95 | 7 | 4.00 | 3.17 |
| Zinc & probiotic | 13 | 2.92 | 19 | 3.32 | 32 | 4.81 | 3.96 |

DISCUSSION

This retrospective study uses medical record data of under five years old of inpatients diagnosed with diarrhea at the Academic Hospital, UGM Yogyakarta from 2021 to 2022. Based on age characteristics, it is known that patients aged 12-23 months have a greater risk of experiencing diarrhea (47%) compared to patients of other ages. This finding is similar to Yusuf¹³ study, which shows that patients under 24 mo of age have a greater risk of diarrhea (58.68%) than patients over 24 mo. Other research also shows that Indonesia's highest cases of diarrhea occur in the age group under 2 years old.¹⁴ The cause of the increased risk of diarrhea in children is generally due to the introduction of breast milk, complementary foods, starting to crawl, the risk of swallowing contaminated materials, and loss of innate immunity from birth.^{15,16}

Although the Integrated Child Health Cluster Service Standards at the Academic Hospital, UGM Yogyakarta and the second guideline, namely the 2017 Clinical Practice Guide in Primary Health Care Facilities, not include probiotics, the results of this study showed that Lacto-B®, which contains probiotic supplements, was most commonly given to children patient. Probiotics probably reduce diarrhea's intensity and duration.⁹ Some probiotics can improve clinical outcomes for acute infectious diarrhea, antibiotic-associated diarrhea, necrotising enterocolitis, IBS, cancer therapies, pouchitis and possibly ulcerative colitis.¹⁷ Probiotics have an important role in the maintenance of immunologic equilibrium in the gastrointestinal tract through the direct interaction with immune cells.¹⁸ Zinc, a mineral supplement, was also widely given in the treatment of diarrhea and according to hospital guidelines regarding the treatment of diarrhea in children. Supplement Zn has been shown to be effective in the treatment of acute diarrhea in several randomized

controlled trials including subsequent meta-analyses.¹⁹ The combination of zinc with cholera vaccine and oral rehydration solution has a positive impact on cholera and diarrhea.²⁰

TABLE 5 shows a significantly relationship between zinc, probiotics, and a combination of zinc and probiotics on the average LoS of under 5 years old patients with diarrhea ($p < 0.05$). Giving zinc alone obtained an average LoS of 3.86 d, giving probiotics alone obtained an average LoS of 3.17 d, and providing a combination of zinc and probiotics obtained an average LoS of 3.98 d. This shows that the group given probiotics alone had a shorter average LoS of 0.69 d (16.56 hr) compared to the group given zinc alone and 0.81 d (19.44 hr) with the group given a combination of zinc and probiotics. The combination of zinc and probiotics took a longer LoS compared to using both in a single condition because in this study there were confounding factors such as antibiotics which could possibly cause differences in the results of the LoS. In this study, the relationship did not take into account the use of antibiotics or other drugs which may be a confounding factor in the results obtained. Because this study focused more on the use of zinc supplementation and probiotics alone or in combination with both. The Integrated Child Health Cluster Service Standards at the Academic Hospital, UGM Yogyakarta state that treating diarrhea with antibiotics is used according to the results of supporting examinations. However, not all patients with diarrhea were given a stool culture examination, which is one of the supporting examinations aimed at finding out whether the patient is infected or not. The present study showed irrational use of antibiotics, and irrational use of antibiotics is still widely practiced in various countries.^{21,22} Furthermore, this could be one of the reasons for the variation in LoS for patients using zinc, probiotics, or a combination of zinc and probiotics who were given antibiotics

alone or in combination.

The study was carried out retrospectively on patient medical record data, therefore, researchers could not observe the patient's actual condition and the completeness quality in the medical record recording. Statistical tests of the relationship between supplements and LoS have not considered confounding variables, such as antibiotics, rehydration fluids, and other antidiarrheal known to influence the average LoS of patients with diarrhea.

CONCLUSION

Patients aged 12-23 mo have a 47% greater risk of experiencing diarrhea compared to other age categories. The classes of drugs used by those under 5 years old of inpatients at the Academic Hospital, UGM Yogyakarta are antidiarrheal (44.50%), rehydration fluids (32.32%), and antibiotics (23.19%). The use of other drugs supported them. Most patients leaving the hospital in an improved condition were allowed to go home (92%). There is a relationship between the use of zinc, probiotics, and a combination of zinc and probiotics on average LoS.

ACKNOWLEDGEMENT

Author would like to thank the Director of Academic Hospital, UGM Yogyakarta for the permission to perform this study.

REFERENCES

1. World Health Organization (WHO). Diarrhoeal disease. [cited 2023 Oct 27]. <https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease>
2. Kelly L, Jenkins H, Whyte L. Pathophysiology of diarrhoea. *Paediatr Child Heal* 2018; 28(11):520-6. <https://doi.org/10.1016/j.paed.2018.09.002>
3. Ministry of Health Republic of Indonesia. Profil Kesehatan

Indonesia 2020.

<https://www.kemkes.go.id/id/profil-kesehatan-indonesia-2020>

4. DIY DK. Profil Kesehatan DIY Tahun 2020.
5. World Health Organization (WHO). Diarrhoea [cited 2023 Oct 27]. https://www.who.int/health-topics/diarrhoea#tab=tab_3
6. Kementerian Kesehatan RI. Diare, tanda gejala dan cara mengatasinya. [cited 2023 Oct 27]. https://yankes.kemkes.go.id/view_artikel/737/diare-tanda-gejala-dan-cara-mengatasinya
7. Lamberti LM, Walker CLF, Chan KY, Jian WY, Black RE. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. *Nutrients* 2013; 5(11):4715-40. <https://doi.org/10.3390/nu5114715>
8. Guarino A, Guandalini S, Vecchio A Lo. Probiotics for prevention and treatment of diarrhea. *J Clin Gastroenterol* 2015; 49:S37-45. <https://doi.org/10.1097/MCG.0000000000000349>
9. Cruchet S, Furnes R, Maruy A, Hebel E, Palacios J, Medina F, et al. The Use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American Experts. *Pediatr Drugs* 2015; 17(3):199-216. <https://doi.org/10.1007/s40272-015-0124-6>
10. Huang R, Xing HY, Liu HJ, Chen ZF, Tang BB. Efficacy of probiotics in the treatment of acute diarrhea in children: a systematic review and meta-analysis of clinical trials. *Transl Pediatr* 2021; 10(12):3248-60. <https://doi.org/10.21037/tp-21-511>
11. Lwanga S, Kaggwa, Lemeshow S. Sample size determination in health studies: a practical manual. Geneva: World Health Organization 1991; viii:80. https://tbrieder.org/publications/books_english/lemeshow_samplesize.pdf
12. Ganiswara. Farmakologi dan terapi.

- Departeman Farmakologi dan Terapeutik FKUI. UI Press; 1995. 831p.
13. Yusuf S. Profil diare di ruang rawat inap anak. *Sari Pediatr* 2016; 13(4):265.
<https://doi.org/10.14238/sp13.4.2011.265-70>
 14. Santika NKA, Efendi F, Rachmawati PD, Has EMM, Kusnanto K, Astutik E. Determinants of diarrhea among children under two years old in Indonesia. *Child Youth Serv Rev* 2020; 111:104838.
<https://doi.org/10.1016/j.chilyouth.2020.104838>
 15. Gedamu G, Kumie A, Haftu D. Magnitude and associated factors of diarrhea among under five children in Farta Wereda, North West Ethiopia. *Qual Prim Care* 2017; 25(4):199207.
 16. Anggraeni R, Aljaberi MAA, Nisha Nambiar N, Sansuwito T Bin, Wati NL. The relationship of supplementary feeding, breast milk (MP-ASI) to infants with the event of diarrhea. *Int J Nurs Inf* 2022;1(1):1-9.
<https://doi.org/10.58418/ijni.v1i1.9>
<https://doi.org/10.53730/ijhs.v6nS4.10072>
 17. Sanders ME, Guarner F, Guerrant R, Holt PR, Quigley EMM, Sartor RB, *et al.* An update on the use and investigation of probiotics in health and disease. *Gut* 2013; 62(5):787-96.
<https://doi.org/10.1136/gutjnl-2012-302504>
 18. Wilkins T, Sequoia J. Probiotics for gastrointestinal conditions: a summary of the evidence. *Am Fam Physician* 2017; 96(3):170-8.
 19. Hoque KM, Binder HJ. Zinc in the treatment of acute diarrhea: current status and assessment. *Gastroenterology* 2006; 130(7):2201-5.
<https://doi.org/10.1053/j.gastro.2006.02.062>
 20. Qadir MI, Arshad A, Ahmad B. Zinc: Role in the management of diarrhea and cholera. *World J Clin Cases* 2013; 1(4):140-2.
<https://doi.org/10.12998/wjcc.v1.i4.140>
 21. Kotwani A, Chaudhury RR, Holloway K. Antibiotic-prescribing practices of primary care prescribers for acute diarrhea in New Delhi, India. *Value Heal* 2012; 15(1 Suppl.):S116-9.
<https://doi.org/10.1016/j.jval.2011.11.008>
 22. Rokhmah NN, Manuel YGP, Putri Kusuma EN, Nurdin NM. The rationality of antibiotics use on acute diarrhea to pediatric inpatients in the Fatmawati Hospital for 2018-2019 Period. *J Farm Galen (Galenika J Pharmacy)* 2022; 8(1):10-21.
<https://doi.org/10.22487/j24428744.2022.v8.i1.15684>