ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 4, 2022

Online - 2455-3891
Print - 0974-2441

Research Article

A RANDOMIZED CONTROLL TRIAL TO COMPARE THE EFFICACY OF *SACCHAROMYCES BOULARDII*, BACILLUS CLAUSII, AND *LACTOBACILLUS RHAMNOSUS* GG PREPARATION IN THE TREATMENT OF ACUTE DIARRHEA IN CHILDREN

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Received: 19 January 2021, Revised and Accepted: 25 February 2022

ABSTRACT

Objective: Probiotics have been recommended as an adjunct to standard treatment of acute diarrhea but the choice of probiotics is unclear. The aim of study is to compare the efficacy of *Saccharomyces boulardii*, *Bacillus clausii* versus *Lactobacillus rhamnosus* in children with acute diarrhea and to expand the tolerability of *S. boulardii*, *B. clausii* versus *L. rhamnosus* GG in acute diarrhea.

Methods: Hospital based Randomized Controlled Clinical trial (chit in box) carried out at the Department of Pediatrics, Mahatma Gandhi Hospital, Jaipur Rajasthan from January 2020 to June 2021. 120 Children were enrolled in the study and randomized to either Group A or Group B or Group C. Group A received *S. boulardii*, Group B received *B. clausii* and Group C received *L. rhamnosus* GG. Sample size was 40 samples for each group. Statistical analysis was done with the SPSS software.

Results: There was statistically significant improvement in consistency observed in Group C as compared to Group A an Group B ($p<0.001$). Significant higher cases (87.5%) were improved in Group C compare to Group B (67.5%), followed by Group A (65%). While all patients were observed well tolerated and accepted during the study.

Conclusions: In our study, *L. rhamnosus* GG significantly reduce the frequency, improve the consistency of stools in diarrhea as compared to *B. clausii* and *S. boulardii* while tolerability of *S. boulardii*, *B. clausii* and *L. rhamnosus* GG was good with no adverse effect.

Keywords: Probiotics, *Saccharomyces boulardii*, *Bacillus clausii*, *Lactobacillus rhamnosus* GG.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i4.44199. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Diarrhea is interpreted as a change in bowel motions for an individual subject identify by arise in the water content, volume, and frequency of stools [1]. This disease is observed over 1400 young kids lose their lives per day, or about 525,000 kids annually, despite the readily availability of an easy and accessible therapeutic solution [2]. In spite of the fact that it is a curable disease, acute diarrhea leavings a major cause of morbidity and mortality in kids worldwide (525,000 deaths in a year among 5 years). Majority of the mortalities took place in developing countries [3].

As per the World Health Organization (WHO) and UNICEF, about to be diarrheal disease cases across the globe every year and 1.9 M kids younger than 5 years die from diarrhea each year, mainly in developing countries. This contributes to 18% of all the deaths of kids <5 years and >5000 kids are dying every day. For such demises, majority as 78% take place in African and Southeast Asian regions [1,2].

Diarrhea is generally a symptom of a contamination in the intestinal tract, due to variety of viral, bacterial and parasitic organisms, spread through contaminated drinking water/food/from person-to-person as an outcome of deficient hygiene. Another common identifiable viral cause of diarrhea is Rotavirus in all kids that belong to *Reoviridae* family, sometimes leads to critical dehydration in infants and children [1]. Probiotics are living micro-organisms that, upon ingestion in definite numbers, deploy health advantages a far inherent general nutrition [4]. It has been propose that probiotics regulate the immune response, build antimicrobial agents and participate in nutrient uptake and adhesion sites with pathogens [5-7]. The WHO suggested and recommended the treatment of acute kid diarrhea with oral rehydration salts and carrying on feeding for the prevention and treatment of dehydration, including zinc supplementation to reduce the duration and severity of the diarrheal episode, with a good safety profile [1]. Probiotics have been recommended as an adjunct to standard treatment, but the choice of probiotics is unclear. Therefore, we have conducted this study with the aim to compare and evaluate the efficacy of *Saccharomyces boulardii*, *Bacillus clausii* versus *Lactobacillus rhamnosus* in kids with acute diarrhea and to expand the tolerability of *S. boulardii*, *B. clausii* versus *L. rhamnosus* GG in decreasing the episodes/day and time frame of acute diarrhea.

METHODS

This study was hospital-based Randomized Controlled Clinical trial (chit in box) conducted at the Department of Pediatrics Mahatma Gandhi Hospital, Jaipur Rajasthan from Jan 2020 to June2021. The study groups included children of 1 month–18 years who were admitted in pediatric ward with complaints of acute diarrhea (duration <14 days) and parents were ready to give written consent. Exclusion criteria were children suffering from dysentery, having evidence of severe malnutrition, signs of any existing illnesses of acute onset (meningitis, sepsis, and pneumonia), immunodeficiency, underlying severe chronic diseases, food allergy or other chronic gastrointestinal diseases, use of probiotics in the last 3 weeks, use of antibiotics or any antimotility medication in the past 3 weeks and during the study, poor compliance (administration of <3 doses of the study medication), and parents were not willing to give written informed consent. After written informed consent were obtained from the parents, detailed medical history taken from children and parents, clinical examination, and laboratory investigations. Subjects who will fulfill the inclusion and exclusion criteria were enrolled in the study and randomized to either As shown in Fig 1, According to flow chart Group A or Group B or Group C. Group A received *S. boulardii*, Group B received *B. clausii*, and Group C received *L. rhamnosus* GG. Sample size was 40 samples for each group. Statistical analysis was done with the SPSS, Trial version 23 version of Windows statistical Software pack (SPS Sinc., Chicago, il, USA) and

Primer. The Categorical significant data were presented as numbers (percent) and comparison made among groups using Chi-square test. The quantitative data were presented as mean and standard deviation and were compared using by Analysis of variance test. Probability $p<0.05$ was considered statistically significant.

RESULTS

Table 1 showed the age distribution of the cases among the group. Most of the cases (49.17%) were observed in age group 5 to 10 followed by <5 years of age (Chi-square=6.844 with degree of freedom; p=0.335). The table also showed the sex distribution of the cases among the group. Most of the cases (53.33%) were observed males. Groups were comparable according to sex (Chi-square=0.469 with 2° of freedom; p=0.791). No significant difference was observed among the groups according to weight (p=0.834). No significant difference was observed among the groups according assessment of dehydration. Out of total 120 children, 45% cases were observed no dehydration followed by 34.17% were some dehydration and 20.83% were with severe dehydration (Chi-square=3.893 with 4° of freedom; p=0.421). Groups were comparable according to age, sex, weight, and dehydration assessment.

Table 2 showed according to consistency of stools, initially all cases were observed with liquid stool, then on day 2 and day 3 there was statistically significant improvement in consistency was observed in Group C as compared to Group A and Group B ($p<0.001$).

Table 3 showed that there was a statistically significant reduction in the frequency of diarrhea within all the groups. There was no significant difference observed among the groups.

Table 4 showed that significant difference was observed among the groups according to improvement/persistence of stool (p=0.045). Significant higher cases (87.5%) were improved in Group C compare to Group B followed by Group A (67.5% and 65%, respectively).

Table 5 showed that all patients were observed well tolerated and well accepted no symptoms were observed of any side effects such as the vomiting, nausea, and abdominal pain during the study period.

DISCUSSION

The first and foremost challenge in picking up a suitable probiotic is the heterogeneity of products accessible from which to pick and the absence of advice on which products may be more successful. Probiotics are explained as live micro-organisms that, when managed in enough amounts, consult a health advantage on the host [8,9]. Nevertheless, the load of evidence for health advantage varies country to country.

In 2013, probiotics were used extensively in Europe and Asia but further use was disallowed on label due to the disparity of proof for multiple claims for health benefits [10]. At present, regulations specific to probiotics are in flux and vary badly from one to another country.

A major cause of morbidity and mortality in developing countries is pediatric acute diarrhea may be due to bacterial or viral etiologies. Latin-American instructions now endorsed some probiotics should be provided with oral rehydration therapy for care of acute pediatric diarrhea [11].

As per the study, 49.17% cases were found in age group of 5–10 years followed by 5 years category. If compared to study by Lahiri *et al*. had kids 2 years, 2–6 years and 6–12 years were 55.7%, 26.7%, and17.5%, respectively [12]. Irfan *et al*. 2017 study showed that 9.8% were in age group 6 months, 10.7% in 6–11 months, 18.9% in 12–23 months, 18.6% in

Table 1: Distribution of cases according to age, gender, weight statistics, and dehydration assessment

Variant	Group A	Group B	Group C	Grand total	p
Age, *n* (%)					
<5	13 (32.5)	16 (40)	13 (32.5)	42 (35.00)	0.335
5–10	22 (55)	14 (35)	23 (57.5)	59 (49.17)	
11–15	4 (10)	9 (22.5)	4 (10)	17 (14.17)	
>15	1 (2.5)	1 (2.5)	0	2 (1.67)	
Total	40 (100)	40 (100)	40 (100)	120 (100.00)	
Mean±SD	6.09±3.53	6.39±4.37	6.42±3.52		0.915
Gender, *n* (%)					
Male	23 (57.5)	21 (52.5)	20 (50)	64 (53.33)	0.791
Female	17 (42.5)	19 (47.5)	20 (50)	56 (46.67)	
Total	40 (100)	40 (100)	40 (100)	120 (100.00)	
Weight (*n*=40), mean±SD	18.69±8.22	18.98±11.36	19.94±9.16		0.834
Assessment of dehydration, *n* (%)					
No	18 (45)	22 (55)	14 (35)	54 (45.00)	0.421
Some	13 (32.5)	11 (27.5)	17 (42.5)	41 (34.17)	
Severe	9 (22.5)	7 (17.5)	9 (22.5)	25 (20.83)	
Total	40 (100)	40 (100)	40 (100)	120 (100.00)	

SD: Standard deviation

Table 2: Comparison of consistency of stool during diarrheal episode among the groups

Consistency of stool	Group A, *n* (%)	Group B, *n* (%)	Group C, *n* (%)	Grand total, *n* (%)	p
Consistency-D1					
Liquid	40 (100)	40 (100)	40 (100)	120 (100)	NA
Consistency-D2					
Liquid	23 (57.5)	19 (47.5)	1 (2.5)	43 (35.83)	<0.001
Semi-solid	17 (42.5)	20 (50)	38 (95)	75 (62.5)	
Solid	0 (42.5)	1 (2.5)	1 (2.5)	2 (1.67)	
Consistency-D3					
Liquid	8 (20)	4 (10)	1 (2.5)	13 (10.83)	<0.001
Semi-solid	31 (77.5)	33 (82.5)	10 (25)	74 (61.67)	
Solid	1 (2.5)	3 (7.5)	29 (72.5)	33 (27.5)	

NA: Not available

Table 3: Mean number of stools (frequency) produced during each day of treatment in children with acute diarrhea among the groups

Duration	Mean±SD			p
	Group A	Group B	Group C	
D1	8.59±2.61	7.30±3.19	8.89±3.13	0.51
D2	6.38±2.74	5.53±2.76	5.45±2.33	0.29
D3	4.30±1.98	4.08±2.04	3.45±2.09	0.157
p	<0.001	<0.001	<0.001	

SD: Standard deviation

Table 4: Improvement/persistence at day 4

Progression	Group A, *n* (%)	Group B, *n* (%)	Group C, *n* (%)	Grand total, *n* (%)	p
Improved	26 (65)	27 (67.5)	35 (87.5)	56 (26)	0.045
Persistence	14 (35)	13 (32.5)	5 (12.5)	64 (14)	

Table 5: Tolerability among the groups

Symptoms	Group A, *n* (%)	Group B, *n* (%)	Group C, *n* (%)	Grand total, *n* (%)
Nausea	0	0	0	0
Vomiting	0	0	0	0
Pain abdomen	0	0	0	0

24–35 months, 21.5% in 36–47 months and 20.5% in 48–59 months [13].

As per the study by Gopchade 2019 found that most frequently affected age group was between 1 and 3 years of age (51.67%) followed by 1 month and 1 year of age (31.67%) [14].

Protection against diarrhea in first 6 month of age group may be give out by many reasons such as maternal antibodies in opposition to enteric pathogens, breastfeeding. It is feasible that post 6 months of age, with the launch of supplementary foods and altering nutritional habits, this defense is lost [15].

In current research work, 53.33% cases were observed in male category. Groups were comparable according to sex. Mostly diarrhea was associated with males, observed by similar outcome reported by Siziya *et al*. (2009) [16]. Lahiri *et al*. 2015 considered 131cases admitted to the pediatric ward where 63.4% were males and rest was females [12]. As per Irfan *et al*., 2017, 51.4% were male and rest was female. Furthermore, as per Gopchade 2019, out of 120 kids, up to the age of 5 years, were 65% boys with M: F ratio of 1:0.53 [13,14]. As per Chakravarthi *et al*., 2019, incidence of acute diarrhea was considered in 54.6% males which were positively linked with diarrhea [17].

As per our study, no significant difference was observed among the groups as per assessment of dehydration. Out of total 120 children, 45% cases were observed no dehydration followed by 34.17% were some dehydration and 20.83% were with severe dehydration. Out of 66 patients with dehydration, 41 patients (62.12%) were diagnosed to be having some dehydration whereas 25 (38.46%) patients were found to have severe dehydration. Similar findings were observed from Gopchade 2019, where out of 120 patients 73.33% cases were treated having some dehydration and 26.67% patients were observed to have severe dehydration [14]. As per Chakravarthi *et al*., 2019, in 39.1% cases severe dehydration was present and some dehydration was present in 60.8% [17].

Therefore, there was a statistically significant reduction in the frequency of diarrhea with in the groups. This shows that these therapies were effective in reducing the frequency of diarrhea. On comparing symbiotic with probiotics on day 1, there was a statistically significant reduction in the frequency of diarrhea (p=0.049). This may probably be due to the effect of symbiotic in reducing the frequency of diarrhea.

According to consistency of stools, initially all cases were observed with liquid stool. On D2 semisolid were observed higher in Group C as compared to both Groups A and B. And D3 similar observation was observed that Group C was better than other two probiotics (p<0.001).

The study of Nista *et al*. (2004) find a more decrease in case of diarrhea in the *B. clausii* group differ with the placebo group after 1 (relative risk [RR] of 0.30; p=0.01) and 2 weeks (RR=0.38) of treatment, decreases the incidences of epigastric discomfort and nausea (p<0.05 for both events) [18]. Plus a meta-analysis on probiotics (*Lactobacillus*, *Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and/or *Bacillus*) for the treatment and prevention of antibiotic associated diarrhea shown a favorable response [19].

Canani *et al*. (2007) found that 1 day post the 1st probiotic administration, the daily count of stools was significantly less (p<0.001) in kids who got *L. rhamnosus* strain GG [20]. As per Keya Lahiri *et al.* (2015) found that *B. clausii* decreased the time, recurrence, and hospital stay of diarrhea thereby decreasing the care and social costs [12]. As per Salloju *et al*. (2017) found that on initial day and stool recurrence were more than 3 times in both groups. On day 3 onward, the episodes was <3 times a day in 14 (35%) of 40 in the *S. boulardii* group and 1 (2.5%) of 40 in the *B. clausii* group (p=0.001). On day 4, *S. boulardii* was 2 times more likely to reduce the frequency of stools to <3/day than *B. clausii* group [21].

The mean stool recurrence/day of rotavirus diarrheal episode was 5.92±2.48 and non-rotavirus 6.73 ± 3.02. As per Ianiro *et al*. (2018) found that a trend of reducing stool recurrence post *B. clausii* administration collate with the control group (mean difference=−0.19 diarrheal motions; 95% CI: −0.43 to −0.06, p0.14). *B. clausii* may constitute an effective therapeutic way in acute childhood diarrhea, with a safe profile [22]. Velasco, María *et al*. (2019) found that the recurrence of stools/day was significantly decreased by day 4 for *S. boulardii* and by day 5 for *L. rhamnosus* GG. [23]. In India, two types of probiotics (*S. boulardii* CNCMI-745 and *L. rhamnosus* GG) significantly compressed both the time of diarrhea and stays in pediatric patients.

De Castro *et al*. 2020 told that information arising from pooled investigation highlighted that *B. clausii* significantly decreased the time of diarrhea (mean difference=−9.12 h; 95% confidence interval [CI]: −16.49−−1.75, p=0.015), and the time of hospitalization (mean difference=−0.85 days; 95% CI: −1.56−−0.15, p=0.017), collate with control [24]. There was a trend of reducing stool recurrence after *B. clausii* administration collate with the control group (mean difference=−0.19 diarrheal motions; 95% CI: −0.43−−0.06, p=0.14). *B. clausii* may show a fruitful therapeutic way in acute childhood diarrhea, with a safe profile [22].

Szajewska H2014 found that *L. rhamnosus* GG (typically at 10^{10} CFU/day for 5–7 days) and *S. boulardii* (typically at 250–750 mg/day [10^{9}–10^{10} CFU] for 5–7 days), for which proof keep up use as adjuncts to rehydration for controlling acute infectious diarrhea in pediatric patients [25]. In our study, significant difference was observed among the groups according to improvement/persistence of diarrhea. Statistically significant (p=0.045) higher cases (87.5%) improved in Group C as compared to Group A (67.5%) and Group B (65%, respectively).

In our study, all patients were observed well tolerated and well accepted no symptoms were observed of any side effects (vomiting, nausea, and abdominal pain) during the study period. This was in correlation with the studies conducted by VanNiel (2002) observed that the effect of various probiotic species and strains on diarrhea was presently well accepted [26]. Boyle *et al*. (2006) where addition of synbiotics did not increase the frequency or severity of Adverse Drug Reactions [27]. Salloju *et al*. (2017) observed that *S. boulardii* and *B. clausii* were well

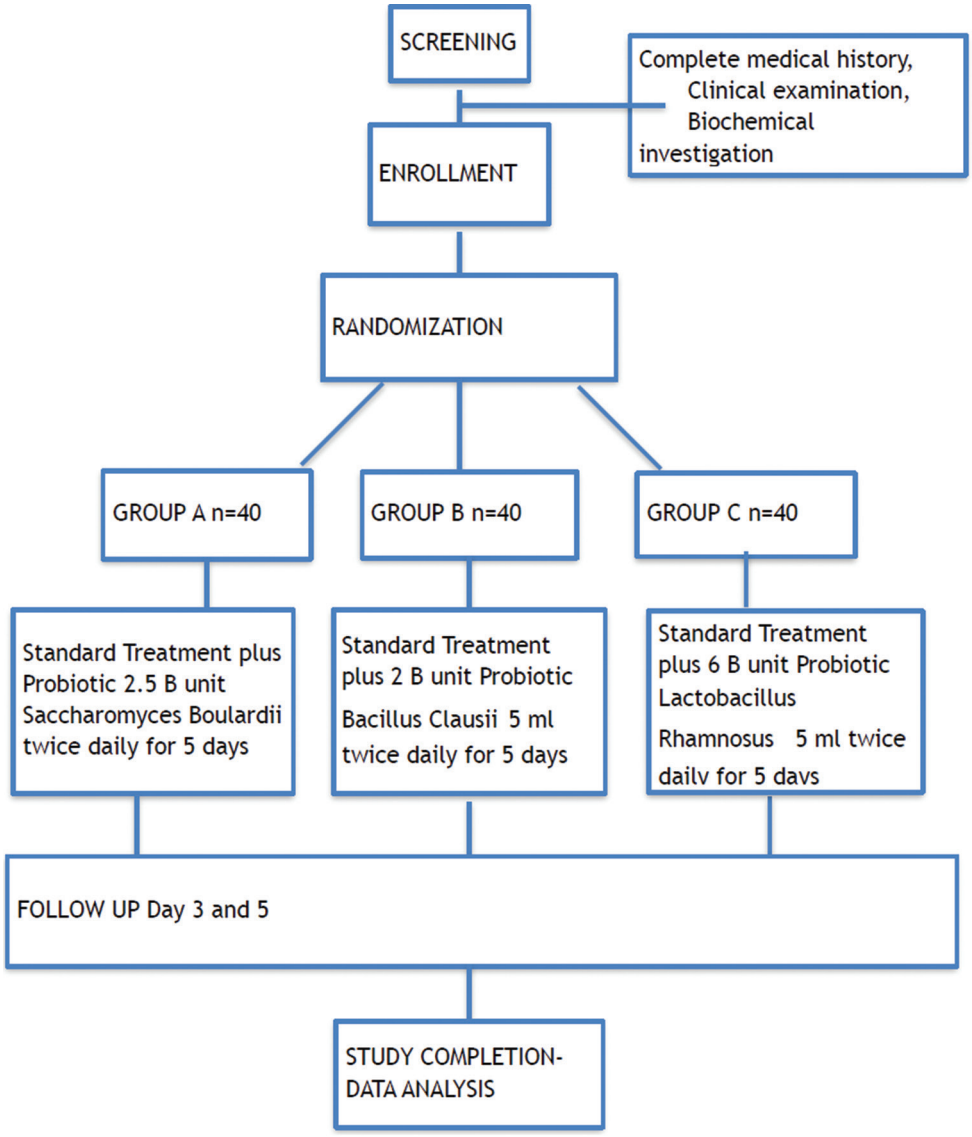

Fig. 1: Study of flow chart

accepted and tolerated by the children and there were no reports of any adverse effects during the study period [21].

Feizizadeh *et al*. (2014) grouped 22 Random controlled trial that treated children with acute diarrhea, but only included studies that used the *S. boulardii* I-745 yeast probiotic. From the shared group data of 17 inquiries that detailed mean time of diarrhea, *S. boulardii* markedly decreased the time by 19.7 h [28]. Szajewska *et al*. (2014) included studies using L. *Acidophilus* LB and observed a statistically significant mean decrease in diarrhea episodes pooled from four trials was 21 h [25].

Strength of study

We compared three probiotics in the same study period in various patients. Hardly any other study could be traced comparing three probiotic in same study.

Limitation of study

Number of cases (sample size) is small in this study. Further study with larger sample size may strengthen the results.

CONCLUSION

This study was conducted with the aim to compare and evaluate the efficacy and tolerability of *S. boulardii*, *B. clausii* versus *L. rhamnosus* GG in the management of acute diarrhea. From the study, we concluded that

1. *L. rhamnosus* GG., *B. clausii*, and *S. boulardii*, all the three probiotics shorten the frequency, while *L. rhamnosus* GG significantly reduce the frequency, improve the consistency and color of stools in diarrhea compared to *B. clausii* and *S. boulardii*.
2. Tolerability of *S. boulardii*, *B. clausii,* and *L. rhamnosus* GG was good with no adverse effect.
3. However, larger studies are needed to extend the clinical application of various probiotics and appropriate dose required to obtain best results.

ACKNOWLEDGMENTS

We are thankful to the department faculty and our patients without their support this study would not have been possible.

FUNDING

No funding sources.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

This study was approved by ethical committee of Mahatma Gandhi Medical College, Jaipur (Letter No.- MGMCH/IEC/JPR/2020/115).

REFERENCES

1. World Health Organization. The Treatment of Diarrhea. A Manual for Physicians and Other Senior Health Workers. Geneva: CDR,World Health Organization; 2005. p. 199.
2. UNICEF. Diarrhoea; 2019. Available from: https://www.data.unicef.org/topic
3. World Health Organization. Diarrhoeal Disease: Fact Sheet; 2017. Available from: http://www.who.int/mediacentre/factsheets/fs330/en [Last accessed on 2018 Mar 02].
4. Guarner F, Schaafsma GJ. Probiotics. Int J Food Microbiol 1998;39:237-8. doi: 10.1016/S0168-1605(97)00136-0
5. Matsuzaki T, Chin J. Modulating immune responses with probiotic bacteria. Immunol Cell Biol 2000;78:67-73. doi: 10.1046/j.1440-1711.2000.00887.x, PMID 10651931
6. Cheikhyoussef A, Pogori N, Chen W, Zhang H. Antimicrobial proteinaceous compounds obtained from bifidobacteria: From production to their application. Int J Food Microbiol 2008;125:215-22. doi: 10.1016/j.ijfoodmicro.2008.03.012, PMID 18514343
7. Abedi D, Feizizadeh S, Akbari V, Jafarian-Dehkordi A. *In vitro* anti-bacterial and anti-adherence effects of *Lactobacillus delbrueckii* subsp bulgaricus on *Escherichia coli*. Res Pharm Sci. 2013;8:260-8. PMID 24082895
8. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al*. Expert consensus document. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014;11:506-14. doi: 10.1038/nrgastro.2014.66, PMID 24912386
9. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al*. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Rev Gastroenterol Hepatol 2014;11:506-14.
10. Miquel S, Beaumont M, Martín R, Langella P, Braesco V, Thomas M. A proposed framework for an appropriate evaluation scheme for microorganisms as novel foods with a health claim in Europe. Microb Cell Factories 2015;14:48. doi: 10.1186/s12934-015-0229-1, PMID 25889559
11. Cruchet S, Furnes R, Maruy A, Hebel E, Palacios J, Medina F, *et al*. The use of probiotics in pediatric gastroenterology: Are view of the literature and recommendations by Latin-American experts. Pediatr Drugs 2015;17:199-216. doi: 10.1007/s40272-015-0124-6
12. Lahiri K, Jadhav K, Gahlowt P, Najmuddin F. *Bacillus clausii* as an adjuvant therapy in acute childhood diarrhoea. IOSR J Dent Med Sci 2015;14:74-6.
13. Irfan M, Zaidi SM, Hira FW. Association of Socio-demographic factors with diarrhea in children less than five years: A secondary analysis of multiple indicator cluster survey sindh. Pak J Publichealth 2014;7:85-9. doi: 10.32413/pjph.v7i2.39
14. Gopchade A. Electrolyte disturbances in children presenting with acute diarrhea: A prospective cohort study. JMSCR 2019;9:777-83.
15. Wilunda MC, Panza A. Factors associated with diarrhea among children less than 5 years old in Thailand: A secondary analysis of Thailand multiple indicator cluster survey 2006. Jhealth Res 2009;23:17-22.
16. Siziya S, Muula AS, Rudatsikira E. Diarrhoea and acute respiratory infections prevalence and risk factors among under-five children in Iraq in 2000. Ital J Pediat 2009;35:1.
17. Chakravarthi GK, Kumar RP. Study on incidences of electrolyte disorders among children with dehydration. Pediatric review. Int J Pediatr Res 2019;6:352-8.
18. Nista EC, Candelli M, Cremonini F, I A Cazzato, M A Zocco, F Franceschi, *et al*. *Bacillus clausii* therapy to reduce side-effects of anti-Helicobacter pylori treatment: Randomized, double-blind, placebo controlled trial. Aliment Pharmacol Ther 2004;20:1181-8.
19. Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, Black RE, Child health epidemiology reference group of the World Health Organization and UNICEF. Global causes of diarrheal disease mortality in children <5 years of age: A systematic review. PLoS One. 2013;8:e72788. doi: 10.1371/journal.pone.0072788, PMID 24023773
20. Canani RB, Cirillo P, Terrin G, Cesarano L, Spagnuolo MI, De Vincenzo A, *et al*. Probiotics for treatment of acute diarrhoea in children: Randomised Clinical Trial of five different preparations. Br Med J 2007;335:340. doi: 10.1136/bmj.39272.581736.55, PMID 17690340
21. Vineet S, Saireddy S, Keerthi T, Mantada PK. Efficacy of *Bacillus clausii* vs Saccharomyces boulardii in treatment of acute rota-viral diarrhea in pediatric patients. Indonesian J Clin Pharm 2017;6:1-6.
22. Ianiro G, Rizzatti G, Plomer M, Lopetuso L, Scaldaferri F, Franceschi F, *et al*. *Bacillus clausii* for the treatment of acute diarrhea in children: A systematic review and meta-analysis of randomized controlled trials. Nutrients 2018;10:1074. doi: 10.3390/nu10081074, PMID 30103531
23. Velasco M, Requena T, Delgado-Iribarren A, Peláez C, Guijarro C. Probiotic yogurt for the prevention of antibiotic-associated diarrhea in adults: A Randomized double-blind placebo-controlled Trial. J Clin Gastroenterol 2019;53:717-23. doi: 10.1097/MCG.0000000000001131, PMID 30439760
24. De Castro JA, Guno MJ, Perez MO. *Bacillus clausii* as adjunctive treatment for acute community acquired diarrhea among Filipino children. A large-scale, multicenter, open-label study (CODDLE). Trop Dis Travel Med Vaccines 2019;5:14. doi: 10.1186/s40794-019-0089-5, PMID 31367461
25. Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, *et al*. Use of probiotics for management of acute gastroenteritis: A position paper by the ESPGHAN Working Group for probiotics and prebiotics. J Pediatr Gastroenterol Nutr 2014;58:531-9. doi: 10.1097/MPG.0000000000000320
26. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. *Lactobacillus* therapy for acute infectious diarrhea in children: A meta-analysis. Pediatrics 2002;109:678-84. doi: 10.1542/peds.109.4.678, PMID 11927715
27. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: What are the risks? Am J Clin Nutr 2006;83:1256-64. doi: 10.1093/ajcn/83.6.1256, PMID 16762934
28. Feizizadeh S, Salehi-Abargouei A, Akbari V. Efficacy and safety of *Saccharomyces* Boulardii for acute diarrhea. Pediatrics 2014;134:e176-91. doi: 10.1542/peds.2013-3950, PMID 24958586