COST-BENEFIT ANALYSIS OF THE PROBIOTIC TREATMENT OF CHILDREN HOSPITALIZED FOR ACUTE DIARRHEA IN BANGKOK, THAILAND

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Abstract. We studied the cost-benefit of using probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) in the treatment of 106 children hospitalized with acute diarrhea using a double-blind randomized, placebo-controlled trial. The median length of hospital stay was significantly shorter in the probiotics group than in the controlled group (2 *vs* 3 days, *p*=0.049), but the median duration of diarrhea and direct medical costs were not significantly different (4 *vs* 5 days, *p*=0.068 and 4,418.75 *vs* 4,778.75 Thai Baht, *p*=0.342). Taking into consideration parental income loss, a non-significant lower expense was seen in the probiotics group (6,800.33 *vs* 7,970.92 Thai Baht, *p*=0.177). A greater cost-benefit with the probiotic treatment is probable, but was not statistically significant in this small study. In conclusion, the probiotics tested shortened the duration of hospitalization of children with diarrhea but the total expenses were not different.

Keywords: probiotics, acute diarrhea, cost-benefit, childhood diarrhea, diarrhea treatment

INTRODUCTION

Acute diarrhea is a global leading cause of mortality and morbidity among children under five years of age (Black *et al*, 2010). Although, the mortality of childhood diarrhea in developed countries is not as high as in developing countries, childhood diarrhea still causes a substantial economic burden (Guarino *et al*, 2012). The cost of a diarrheal episode is high. In 2001-2002, the direct medical cost of treating a child with diarrhea in Thailand was about 2,100 Thai Baht (THB) [approximately 52 US dollars (USD)] per hospitalization (Intusoma *et al*, 2008). In Europe, the estimated total societal cost, including both direct medical and indirect costs, per one rotavirus diarrheal infection during 2004-2005 ranged from 166 to 2,101 Euros, depending on the setting (Giaquinto *et al*, 2007).

Rehydration therapy is key and should be started promptly. However, rehydration therapy does not decrease the severity or shorten the duration of diarrhea (Guarino *et al*, 2012). Some adjunctive pharmacotherapies might be effective in reducing symptoms and the burden of acute childhood diarrhea (Guarino *et al*, 2012). Probiotics, live microorganisms that provide benefits for the health of the host when administered in adequate

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doses (Joint FAO/WHO Working Group, 2002), are among the adjunctive therapies that have shown some clinical benefit in treating acute childhood diarrhea (Allen *et al*, 2010). Probiotics with proven efficacy and in appropriate doses have been recommended as adjunctive treatment in addition to rehydration therapy for acute diarrhea in children (Guarino *et al*, 2008). Several meta-analyses found specific probiotic strains can significantly reduce the duration of diarrhea by at least one day (Van Niel *et al*, 2002; Szajewska *et al*, 2007a,b).

A probiotic combination of *Lactobacillus acidophilus* and *Bifidobacterium* spp has been used effectively in treating acute childhood diarrhea (Lee *et al*, 2001; Vivatvakin and Kowitdamrong, 2006; Rerksuppaphol and Rerksuppaphol, 2010) but data about its cost-effectiveness are scarce. The objectives of this study were to evaluate the cost-benefit of using a probiotic combination (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) to treat children hospitalized because of acute diarrhea, to assess the duration of illness and its acceptability among patients and parents.

MATERIALS AND METHODS

Subjects

This study was conducted at the Department of Pediatrics, Phramongkutklao Hospital, Thailand from April 2010 to September 2011. Children from 3 to 72 months of age who were hospitalized due to acute diarrhea and whose parents consented to participate were eligible for the study. Acute diarrhea was defined as passing at least three liquid or loose stools, or one large amount of watery stool within 24 hours, but lasting no longer than seven days prior to the hospitalization. Children who had been previously treated during this diarrheal episode with either probiotics or another antidiarrheal drug (*ie*, kaolin, pectin, smectite, activated charcoal, racecadotril or cholestyramine) or who had other gastrointestinal diseases, chronic diseases or severe dehydration were excluded.

Study design

The study was a randomized, double-blind, placebo-controlled clinical trial. Parents were informed of the objectives of the study by one of the investigators and their written consent was obtained prior to data collection. Demographic data, including age, sex, body weight, parental income, duration of diarrhea prior to hospitalization, numbers of stools in the previous 24 hours and stool characteristics, were collected. The patient was then randomly allocated into either the treatment (probiotics) or the control (placebo) group and given standard treatment for acute diarrhea with rehydration therapy (orally and intravenously) along with the probiotics (a combination of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* under the trade name of Infloran®) or a placebo. Randomization was made using software and the identifications of the study groups were kept in sealed envelopes. Antimicrobials were prescribed according to the attending pediatrician's clinical judgement. Stool was obtained for bacterial culture and rotavirus antigen (using an ELISA technique) when practicable.

The probiotics and placebo and partial financial support for this study were provided by Laboratorio Farmaceutico SIT. Each probiotic capsule contained a minimum of one billion organism of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* viv. lyophilisat with lactose and

magnesium stearate as excipients. The placebo containing only the excipients was in an identical appearing capsule. Children aged <1 year were given one capsule twice daily while those aged >1 year were given one capsule three times daily until the cessation of diarrhea, but no longer than seven days. The contents of the capsules could be mixed with water if the child was not able to swallow the capsule whole.

The outcomes measured were direct medical costs [hospital and service expenses, as well as the drug cost in Thai Baht (THB)], total cost (direct medical cost and indirect cost, *ie*, estimated parental income loss), length of stay (in days), duration of illness (in days), and drug acceptability. The first day of hospitalization was counted as one day only if the patient was admitted before 4:00 PM, while the discharge day was counted as one day only if the patient left after 12:00 PM. Patients were discharged after recovery, defined by either the patient passing no stools for at least 12 hours or passing formed stools. The ratio of the cost and the inverse of the length of hospital stay (in THB-day) was used as a cost-benefit index. A smaller index would reflect a greater cost-benefit for the treatment. The drug acceptability was rated by the parents using a score of 0 to 5, from least favorable to most favorable.

This study was approved by the Royal Thai Army Medical Department Institutional Review Board (RTA MD IRB) prior to being conducted. All procedures and measures were carried out in accordance with the Helsinki Declaration.

Statistical analysis

The sample size was calculated using G power software, version 3.0.5 (by Franz Faul, University Kiel, Germany). We assumed the estimated cost per one diarrheal episode was around THB4,000 (approximately USD133.33). A sample size of 100 was required (50 in each group) to detect a 25% difference in the cost between the groups with a p-value < 0.05 and a power = 0.9. Descriptive data were presented as medians (including range or inter-quartile range) and percentages. The chi-square and Mann-Whitney U test were used to test differences between the two groups.

RESULTS

One hundred six patients were enrolled in the study with 53 patients in each group. A summary of the demographic data is shown in Table 1. The two groups (study and control groups) were comparable. The duration of diarrhea and number of stools during the 24 hours prior to admission were not significantly different between the two groups. Rotavirus infection was identified in 36 of 104 children (34.6%); the prevalence was not different between the two groups. Bacterial pathogens were identified in 15.3% of subjects; the prevalence of bacterial infection was lower in the study group (8% *vs* 22% in the control group, p=0.05). The most common pathogens found were *Salmonella* species, *Plesiomonas shigelloides* and *Aeromonas* species. The use of antimicrobials and changing to a lactose free formula were not significantly different between the two groups. The median duration of hospitalization was significantly shorter by one day in the children receiving probiotics than the children receiving the placebo (Table 2). However, no significant difference in duration of illness was found between the two groups.

The direct medical costs (hospital charges and drug costs) were not significantly lower (p=0.342) in the treatment

Table 1
Characteristics of study patients.

	Probiotics group (N=53)	Placebo group (N=53)	p-value
General ward : deluxe ward	22:31	22:31	1.000[a]
Age (months)[b]	15 (4-72)	19 (6-64)	0.185[c]
Male gender (%)	58.5	52.8	0.558[a]
Weight (kg)[b]	9.4 (6.5-23.3)	10.2 (6.2-20)	0.251[c]
Duration of diarrhea prior to admission (days)[b]	2 (0-7)	2 (0-6)	0.606[c]
Number of stools in previous 24 hours[b]	6 (3-25)	6 (1-20)	0.799[c]
Stool characteristic			
Watery (%)	90.6	86.8	0.539[a]
Mucus/bloody (%)	9.4	13.2	
Causative agents:			
Rotavirus (%)	39.6	29.4	0.274[a]
Bacteria (%)	8.2	22.4	0.05[a]
Vomiting (%)	79.2	88.7	0.186[a]
Parental monthly income [b] (THB)	20,000 (4,000-60,000)	20,000 (6,000-250,000)	0.729[c]

THB, Thai Baht. One US dollar equals THB 30. [a]Chi-square test. [b]Values are presented in median (range). [c]Mann-Whitney U test.

Table 2
Hospitalization data.

	Probiotics group (N=53)	Placebo group (N=53)	p-value
Antimicrobial treatment, n (%)	10 (18.9)	12 (22.6)	0.632[a]
Lactose free formula, n (%)	6 (11.3)	7 (13.2)	0.767[a]
Duration of illness (days)[b]	4 (3-6)	5 (4-6)	0.068[c]
Length of hospitalization (days)[b]	2 (2-3)	3 (2-4)	0.049[c]
Drug acceptability rating score[b]	4 (4-5)	4 (4-5)	0.869[c]

[a]Chi-square test. [b]Values are presented in median (inter-quartile range). [c]Mann-Whitney U test.

group than in the control group (THB 4,418.75 vs 4,778.75). When taking parental income loss into consideration, the treatment group had a non-significantly lower loss (p=0.177) than the control group (THB 6,800.33 vs 7,970.92). A similar finding was also seen for cost-benefit (Table 3). The average price of the probiotics was THB 17/capsule, or THB 34 per day for infants and THB 51 per day for older patients.

No serious adverse effects due to the probiotics or placebo were seen in the study. The acceptability of drug was good in both groups (p=0.869).

DISCUSSION

Probiotics have been shown to be of benefit in treating acute childhood diarrhea (Guarino et al, 2008; Floch et al, 2011).

Table 3
Cost-benefit comparison.

	Probiotics group Median (IQR)	Placebo group Mediabn (IQR)	*p*-value
Direct medical cost (THB)	4,418.75 (3,547-5,856)	4,778.75 (3,639.25-6,779.50)	0.342
Cost-benefit index (THB-day)	10,838.5 (7,037-18,386)	15,108 (7,278.5-23,213.25)	0.138
Direct medical costs and parental income loss estimated from daily minimum wage (THB 203/day in year 2010)	5,230.75 (4,279-6,638.25)	5,773 (4,370.75-7,997.5)	0.368
Cost-benefit index (THB-day)	12,930 (8,312-21,999)	18,153 (8,239-26,258.25)	0.132
Direct medical costs and parental income loss estimated from amount reported by parents (THB)	6,800.33 (5,321.50-11,237.83)	7,970.92 (5,781.08-11,504)	0.177
Cost-benefit index (THB-day)	18,232.17 (10,008-29,946.5)	22,777 (14,134-46,016)	0.089

THB, Thai Baht. One US dollar approximately equals THB 30. Values are presented in median (inter-quartile range). Statistics were analyzed using the Mann-Whitney *U* test.

Effective strains include *Lactobacillus rhamnosus* GG (Szajewska *et al*, 2007b), *Saccharomyces boulardii* (Szajewska *et al*, 2007a), *Lactobacillus reuteri* (Shornikova *et al*, 1997) and a combination of *L. delbrueckii* var *bulgaricus, Streptococcus thermophilus, L. acidophilus*, and *Bifidobacterium bifidum* (Canani *et al*, 2007). Most probiotics reduced the duration of diarrhea by approximately one day. This adjunctive therapy may cost more than oral rehydration solution and cost-benefit data are scarce. In our study, the combination of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* had modest beneficial effect on shortening hospitalization due to acute childhood diarrhea. The higher prevalence of bacterial pathogens in our study placebo group might have had an impact on the results. The main focus of the study was the cost-benefit of probiotics, not the recovery time.

Hospital admission and discharge criteria were not specified in this study and were up to the clinician. To avoid bias, the physicians, researchers and participants were blinded to the type of treatment. The length of hospitalization was classified as days and not hours, which could affect the sensitivity of the study.

The probiotics did not result in an overall higher direct medical cost, although there was an additional cost of the probiotics. It did result in an overall non-significantly lower cost of hospitalization. This non-significant difference might be due to the small margin of difference in cost and cost-benefit between the two groups. For example, the median direct medical cost was only 8% smaller in the treatment group than the control group. The difference was 17% for the model that included reported parental income. Our estimated sample size was based on

a 25% difference in cost. The small sample size gave inadequate power to determine a significant difference with this small difference in costs.

A study from Belgium found synbiotics containing fructo-oligosaccharide and probiotic strains can reduce the health care costs in children with acute gastroenteritis in spite of the higher cost of the probiotic (Vandenplas and De Hert, 2012). This savings was based on the assumption of fewer consultations and use of concomitant medications. Our study was conducted in a governmental hospital where there are no consultation fees. This may result in a smaller margin of difference than expected. Our study did not evaluate health care costs at private hospitals in Thailand, where extra professional fees might be incurred.

The burden of acute childhood diarrhea includes not only direct medical costs but also indirect costs, such as productivity loss and the value of workdays lost based on the average wages of parents. Each year, the economic burden estimated as the direct medical and indirect costs of acute diarrhea, especially rotavirus gastroenteritis, is high in both developing and developed countries (Giaquinto *et al*, 2007; Ogilvie *et al*, 2012). In our study, the cost-benefit of probiotics was greater when indirect costs were included, although it was not statistically significant. It is reasonable to assume a larger study population could have shown a significant benefit due to probiotic treatment.

Effective treatment for diarrhea to reduce the severity of symptoms and to prevent hospitalizations are needed globally. Although this study did not show a significant cost-benefit, a non-significant benefit in lowering cost was seen and a larger study population may have shown

a significant cost-benefit. Further studies in different settings, such as outpatient clinics, emergency departments and private hospitals are needed to evaluate the cost-benefit of probiotics in various settings.

In conclusion, the probiotics studied resulted in a shorter duration of hospitalization in acute childhood diarrhea by one day but did not have a significant effect on cost.

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REFERENCES

Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev* 2010: CD003048.

Black RE, Cousens S, Johnson HL, *et al.* Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010; 375: 1969-87.

Canani RB, Cirillo P, Terrin G, *et al.* Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ* 2007; 335: 340.

Floch MH, Walker WA, Madsen K, *et al.* Recommendations for probiotic use-2011 update. *J Clin Gastroenterol* 2011; 45 (suppl): S168-71.

Giaquinto C, Van Damme P, Huet F, Gothefors L, Van der Wielen M. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. *J Infect Dis* 2007; 195 (suppl 1): S36-44.

Guarino A, Albano F, Ashkenazi S, *et al.* European Society for Paediatric Gastroenterol-

ogy, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. *J Pediatr Gastroenterol Nutr* 2008; 46 (suppl 2): S81-122.

Guarino A, Dupont C, Gorelov AV, *et al.* The management of acute diarrhea in children in developed and developing areas: from evidence base to clinical practice. *Expert Opin Pharmacother* 2012; 13: 17-26.

Intusoma U, Sornsrivichai V, Jiraphongsa C, Varavithaya W. Epidemiology, clinical presentations and burden of rotavirus diarrhea in children under five seen at Ramathibodi Hospital, Thailand. *J Med Assoc Thai* 2008; 91: 1350-5.

Joint FAO/WHO Working Group. Report on drafting guidelines for the evaluation of probiotics in food. London, Ontario: FAO/WHO, 2002.

Lee MC, Lin LH, Hung KL, Wu HY. Oral bacterial therapy promotes recovery from acute diarrhea in children. *Acta Paediatr Taiwan* 2001; 42: 301-5.

Ogilvie I, Khoury H, Goetghebeur MM, El Khoury AC, Giaquinto C. Burden of community-acquired and nosocomial rotavirus gastroenteritis in the pediatric population of Western Europe: a scoping review. *BMC Infect Dis* 2012; 12: 62.

Rerksuppaphol S, Rerksuppaphol L. *Lactobacil-lus acidophilus* and *Bifidobacterium bifidum* stored at ambient temperature are effective in the treatment of acute diarrhoea. *Ann Trop Paediatr* 2010; 30: 299-304.

Shornikova AV, Casas IA, Isolauri E, Mykkanen H, Vesikari T. *Lactobacillus reuteri* as a therapeutic agent in acute diarrhea in young children. *J Pediatr Gastroenterol Nutr* 1997; 24: 399-404.

Szajewska H, Skorka A, Dylag M. Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhoea in children. *Aliment Pharmacol Ther* 2007a; 25: 257-64.

Szajewska H, Skorka A, Ruszczynski M, Gieruszczak-Bialek D. Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. *Aliment Pharmacol Ther* 2007b; 25: 871-81.

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.

Vandenplas Y, De Hert S. Cost/benefit of synbiotics in acute infectious gastroenteritis: spend to save. *Benef Microbes* 2012; 3: 189-94.

Vivatvakin B, Kowitdamrong E. Randomized control trial of live *Lactobacillus acidophilus* plus *Bifidobacterium infantis* in treatment of infantile acute watery diarrhea. *J Med Assoc Thai* 2006; 89 (suppl 3): S126-33.