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Factors Associated With Nonadherence in an Emergency Department-based Multicenter Randomized Clinical Trial of a Probiotic in Children With Acute Gastroenteritis

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Abstract

Nonadherence in clinical trials affects safety and efficacy determinations. Predictors of nonadherence in pediatric acute illness trials are unknown. We sought to examine predictors of nonadherence in a multicenter randomized trial of 971 children with acute gastroenteritis receiving a 5-day oral course of *Lactobacillus rhamnosus* GG or placebo. Adherence, defined as consuming all doses of the product, was reported by the parents and recorded during daily follow-up contacts. Of 943 patients with follow-up data, 766 (81.2%) were adherent. On multivariate analysis, older age (OR 1.19; 95% CI: 1.00–1.43), increased vomiting duration (OR 1.23; 95% CI: 1.05–1.45), higher dehydration score (OR 1.23, 95% CI: 1.07–1.42), and hospitalization following ED discharge (OR 4.16, 95% CI: 1.21–14.30) were factors associated with nonadherence; however, those with highest severity scores were more likely to adhere (OR 0.87, 95% CI: 0.80–0.95). These data may inform strategies and specific targets to maximize adherence in future pediatric trials.

Keywords

acute gastrointestinal infections; compliance; study participants

Nonadherence, defined as failure to take medications with respect to timing, dosage, and frequency during the prescribed length of time (1), is a common and significant problem in clinical practice, and has been linked to poor patient outcomes and increased health care costs (2,3). There are many known causes of nonadherence in clinical practice, including cost and complexity of treatments, disruption to patient's routines, poor understanding of benefits and risks, as well as medication side effect (particularly when treating chronic conditions) as well as complex interactions between patient, provider and health care system factors (1,4). In children, additional challenges include the need for a devoted and dedicated caregiver, developmental constraints in obtaining cooperation from young patients, and the psychological and lifestyle challenges experienced in adolescence (5). Despite these challenges, the average rate of adherence in children with chronic conditions is like that of adults, about 50%, but with declining adherence reported with time (6). Published rates for adherence with medications prescribed from pediatric EDs for acute illnesses range between 65% and 72% in the United States (7,8) and over 90% in Canada (9). Factors associated with nonadherence in the ED setting included older age, having public insurance (8), dissatisfaction with explanations, instructions for treatment, and follow-up (9).

In general, the average adherence in clinical trials is thought to be higher than in clinical practice given selection and close attention to participants and incentives from study personnel; however, average adherence rates can vary significantly and decrease over time

(10). In a clinical trial, nonadherence can result in confounding of safety and efficacy results, lower study power, and reduce the magnitude of treatment effect. Methodological and statistical strategies have been described to mitigate the effects of nonadherence on clinical trials; however, the reasons for nonadherence in clinical trials are not fully understood (11). They likely include similar causes as in clinical practice, and potentially artifactual nonadherence, such as enrolling in multiple studies, pretending to have certain conditions, or lying about adherence to collect stipends and incentives (12).

To the best of our knowledge, there are no data regarding risk factors for nonadherence in acute illness pediatric trials, and specifically probiotics, which are thought in general to be beneficial and safe. To address this knowledge gap, we aimed to determine factors associated with nonadherence of a probiotic product in a randomized, placebo-controlled trial in 971 patients 3–48 months of age with acute gastroenteritis (AGE).

METHODS

This is a secondary analysis of the multicenter Pediatric Emergency Care Applied Research Network (PECARN) Probiotic Study (13). Briefly, this prospective, randomized, parallel-group, double-blind trial included 971 children 3 to 48 months of age who presented with AGE to 10 US pediatric EDs between July 2014 and June 2017. The study was approved by all study site institutional review boards. Eligible participants were diagnosed as having AGE defined as 3 or more watery stools per day, with or without vomiting, for fewer than 7 days. Children were excluded if they or their direct caregivers had risk factors for bacteremia (ie, immunocompromised, used systemic steroids in the past 6 months, presence of an indwelling catheter, known structural heart disease, history of prematurity who were younger than 6 months at enrollment) or a chronic gastrointestinal disorder (eg, inflammatory bowel disease). Additional exclusion criteria were presence of pancreatitis, bilious emesis, hematochezia, known allergy to LGG, microcrystalline cellulose, erythromycin, clindamycin, or β-lactam antibiotics (these antibiotics might have been used to treat an invasive infection caused by LGG).

Participants received either a 5-day course of 1×10^{10} CFU of LGG or a placebo of similar appearance and taste. The contents of the product were sprinkled in 30mL of noncarbonated room temperature liquid. The first dose of the product was administered in the ED and caregivers were instructed to give subsequent doses and to complete daily diaries of symptoms at home. Follow-up surveys were coordinated centrally by the lead site and completed daily by email or phone for 5 days (symptoms, side effects, and adherence) and again 14 days (symptoms and side effects) and 1 month (side effects) after enrollment. Participants were compensated $10 USD for each follow-up phone call or survey completed. Adherence data were reported by caregivers and collected during daily contacts. Care givers were given a letter explaining the trial for their primary care provider or for any other non-research team provider and instructed to produce the letter, in case medical treatment was required during the study period. Instructions regarding the protocol were shared with in-patient teams for those participants directly admitted to the hospital from the ED and research personnel ensured continued monitoring of symptoms on those patients during hospitalization. Side effects were defined as the occurrence of a priori identified

specific symptoms reported within a month of enrollment: bloating, gas, intestinal rumbling, diarrhea, visible blood in stool, abdominal pain, abdominal cramps, nausea, vomiting, loss of appetite, heartburn, constipation, skin rash, diaper rash, fever, nasal congestion, runny nose, sore throat, cough, headache, muscle aches, chills, or weakness. We reported side effects according to the International Conference on Harmonization guideline for Good Clinical Practice. Degree of dehydration was determined by the Clinical Dehydration Score and disease severity was classified using the Modified Vesikari Scale score (13).

The primary outcome of this study was adherence, as reported on the survey conducted at day #5. Parents were asked how many doses were given and to count the number of doses remaining, if any. Participants were deemed to be fully adherent if they consumed all 10 doses provided (ie, 100%).

We used multiple imputation methods in cases where information needed to derive the primary outcome was incomplete. The imputations were obtained by fitting a sequence of regression models and drawing values from the corresponding predictive distributions (13,14). We describe summary statistics of the sample by adherence group. Continuous variables were summarized using the median (IQR) and compared between groups using the Wilcoxon rank sum test. We summarized using the median (IQR) or mean (SD) categorical variables using proportions, compared groups using the chi-square test of association, and assessed independent factors associated with nonadherence using logistic regression using backwards elimination, adjusting for site and symptom duration. Candidate factors included all variables with a univariable 2-sided *P* value <0.2 along with pre-determined variables of interest. The cut-off probability for remaining in the model was <0.10. We used IVE ware software (University of Michigan) for imputation and SAS software, version 9.4 (SAS Institute), for all other analyses.

RESULTS

Of 3143 patients meeting inclusion criteria, 2172 were excluded (744 had 1 or more exclusion criteria; 262 were not approached; 1155 did not consent; and 11 were not randomized). Nine hundred seventy-one participants were enrolled in the study of which 28 were lost to follow-up, 943 were included in this analysis, and 766 (81.2%) consumed all doses of the study product. Although the degree of missingness differed among variables, <1% of the total data used in the analyses were imputed (Supplemental Table, http://links.lww.com/MPG/B929). In univariable analyses, participant demographics and baseline characteristics, including age, race, ethnicity, median income, seasonality, site, follow-up method, duration, and severity of vomiting were similar between the nonadherent and adherent groups except for higher dehydration scores (0.8 vs 0.6, *P*=0.005) and higher proportion admitted to hospital following ED discharge (4.3% vs 1.1% *P*=0.013) in the nonadherent group (Table 1). On multivariable analysis, older age (OR 1.19; 95% CI: 1.00–1.43 per 1 year increase), increased vomiting durations at baseline (OR 1.23; 95% CI: 1.05–1.45 per 1 day of vomiting increase), higher dehydration score (OR 1.23, 95% CI: 1.07–1.42 per 1 point increase), and hospitalization following ED discharge (OR 4.16, 95% CI: 1.21–14.30) were factors associated with nonadherence. Those with higher baseline AGE severity at presentation (ie, higher baseline Modified Vesikari Scale score; OR 0.87,

95% CI: 0.80–0.95) were less likely to be nonadherent to the treatment (Table 2). Overall side effects reported at follow-up were similar between the groups, although individually, the presence of rhinorrhea was more common in patients adherent with treatment (8.9% vs 3.4%, $P = 0.02$)).

DISCUSSION

In this large randomized placebo-controlled trial of a probiotic in children with acute gastroenteritis, we found a low rate of self-reported nonadherence (18.8%). Factors associated with nonadherence in this trial included older age, increased duration of vomiting, higher dehydration scores at baseline and hospitalization following ED discharge. Although several of these parameters reflect individual elements of disease severity, we also found that patients with higher baseline overall disease severity scores were more likely to be adherent with the prescribed intervention.

These results, pertinent to the populations studied, are important as, to the best of our knowledge, factors associated with nonadherence in a pediatric ED-based trial for an acute illness have not been previously reported. Furthermore, the product was a probiotic, which is typically considered to have minimal or no side effects and is often provided by caregivers to their children during episodes of diarrheal illness (15). Although many of these factors are not easily modifiable, clinicians and researchers can use this knowledge to inform strategies to maximize adherence in future trials, such as focusing on managing toddler specific behavior (refusal to take medication by spitting or pursing lips), or foreseeing issues related to vomiting or better preparing for instances in which patients may be re-admitted to the hospital, among others.

Not surprisingly, participants with characteristics that may impair oral intake, such as vomiting and dehydration were less likely to adhere to the treatment, as well as older patients who may theoretically offer more resistance to taking oral medication. In this context, it may be counterintuitive that those with higher severity scores at baseline were more likely to adhere to the treatment. This may be explained by the fact that the severity score includes multiple individual elements not necessarily related to the ability to take oral medications, such as diarrhea duration and severity, fever among others (13).

It was interesting to note that patients who were initially sent home from the ED and subsequently returned and were admitted to the hospital were less likely to complete the treatment. This could relate to patients forgetting the medication at home or a lack of desire by the inpatient physician to continue the study intervention because of perceived lack of efficacy or side effects. Although there were few of these patients in our trial, and it is difficult to predict which patients will be readmitted after ED discharge, our findings highlight the importance of considering the potential impact of admission on adherence to medication administration of ED-initiated trials. Means to ensure study interventions continue when children are admitted to the hospital at the index visit or subsequently should be planned.

Limitations of this analysis included that we relied on self-report of adherence, and we did not collect self-reported reasons for nonadherence. Also, the results do not necessarily apply to routine clinical care given the attention and incentives to participants as well as frequent follow-up contacts in RCTs. Our results, however, can inform future pediatric interventional trials in the ED setting.

CONCLUSIONS

Nonadherence occurred more frequently in older patients, in those with symptoms potentially diminishing the ability to consume oral medications and those hospitalized after ED discharge. Patients with higher disease severity scores at baseline were, however, more likely to adhere to treatment. These data may inform strategies and specific targets to maximize adherence in future pediatric ED-based trials. Future research may focus on more comprehensive understanding of self-reported causes of nonadherence and the development of joint strategies to maximize adherence in trials and in clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The Food and Drug Administration granted an Investigational New Drug approval (IND#12371). iHealth Inc. provided *L rhamnosus* GG and placebo capsules at no cost but had no involvement in the conduct or reporting of the trial.

D.S. received in-kind study drug and placebo from iHeath Inc.; however, the company did not contribute financially to the study or to the investigators, and their employees do not have access to study data. IHealth personnel had no role in study design, collection management, analysis and interpretation of data nor did they have any role or authority in writing the report nor decision to submit the trial for publication.

REFERENCES

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–97. [PubMed: 16079372]
2. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy 2014;7:35–44. [PubMed: 24591853]
3. Blaschke TF, Osterberg L, Vrijens B, et al. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol 2012;52:275–301. [PubMed: 21942628]
4. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004;42:200–9. [PubMed: 15076819]
5. Matsui D Current issues in pediatric medication adherence. Paediatr Drugs 2007;9:283–8. [PubMed: 17927300]
6. El-Rachidi S, LaRochelle JM, Morgan JA. Pharmacists and pediatric medication adherence: bridging the gap. Hosp Pharm 2017;52:124–31. [PubMed: 28321139]

7. Sammons NW, Yin H. Compliance of medications prescribed from a pediatric emergency department. Pediatr Emerg Care 2015;31:399–402. [PubMed: 25996233]

8. Kajioka EH, Itoman EM, Li ML, et al. Pediatric prescription pick-up rates after ED visits. Am J Emerg Med 2005;23:454–8. [PubMed: 16032610]

9. Matsui D, Joubert GI, Dykxhoorn S, et al. Compliance with prescription filling in the pediatric emergency department. Arch Pediatr Adolesc Med 2000;154:195–8. [PubMed: 10665609]

10. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. Clin Pharmacol Ther 2014;95:617–26. [PubMed: 24739446]

11. Shiovitz TM, Bain EE, McCann DJ, et al. Mitigating the effects of nonadherence in clinical trials. J Clin Pharmacol 2016;56:1151–64. [PubMed: 26634893]

12. Devine EG, Waters ME, Putnam M, et al. Concealment and fabrication by experienced research subjects. Clin Trials 2013;10:935–48. [PubMed: 23867223]

13. Schnadower D, Tarr PI, Casper TC, et al. Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. N Engl J Med 2018;379:2002–14. [PubMed: 30462938]

14. Raghunathan TELJ, Van Hoewyk J, Solenberger P, et al. A multivariate technique for multiply imputing missing values using a sequence of regression models. Survey Methodol 2001;27:85–95.

15. Li ST, Klein EJ, Tarr PI, et al. Parental management of childhood diarrhea. Clin Pediatr (Phila) 2009;48:295–303. [PubMed: 19023110]

What Is Known

- In clinical practice, nonadherence (defined as failure to take medications as prescribed) is linked to poor clinical outcomes.
- In research, nonadherence results in potentially biased results.
- Factors associated with nonadherence have not been described in pediatric acute care trials.

What Is New

- In a large randomized controlled trial of probiotics in children with acute gastroenteritis, nonadherence was independently associated with older age, with the presence of symptoms potentially diminishing the ability to consume oral medications and with return hospitalization after emergency department discharge.
- These data may inform strategies to minimize nonadherence in future pediatric trials and in clinical practice.

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TABLE 1.

Demographics and baseline characteristics

	Did subject complete all 10 doses			
	Yes (N = 766) (81.2%)	**No (N = 177) (18.8%)**	**Overall (N = 943)**	***P* value**
Treatment arm				0.45
Probiotic	376 (49.0%)	93 (52.2%)	468 (49.6%)	
Placebo	390 (51.0%)	84 (47.8%)	474 (50.4%)	
Sex: male	406 (53.1%)	98 (55.1%)	504 (53.4%)	0.57
Age: median (Q1, Q3)	1.4 (0.9, 2.3)	1.5 (0.9, 2.5)	1.4 (0.9, 2.3)	0.07
Race				0.69
White	241 (31.5%)	53 (29.7%)	294 (31.2%)	
Black or African American	273 (35.7%)	62 (34.9%)	335 (35.5%)	
Multiracial/other race	51 (6.7%)	14 (7.7%)	65 (6.9%)	
Unknown/not reported	200 (26.1%)	49 (27.7%)	249 (26.4%)	
Ethnicity				0.74
Hispanic or Latino	282 (36.8%)	67 (37.8%)	349 (37.0%)	
Not Hispanic or Latino	468 (61.2%)	105 (59.0%)	573 (60.8%)	
Unknown or not reported	15 (2.0%)	6 (3.2%)	21 (2.2%)	
Median income (dollars) (zip code): median (Q1, Q3)	$41,742.50 ($31,212.30, $55,783.20)	$41,354.40 ($30,186.90, $56,685.10)	$41,621.10 ($31,051.00, $55,961.80)	0.50
Enrollment Season				0.96
Winter	179 (23.4%)	38 (21.2%)	217 (23.0%)	
Spring	254 (33.1%)	62 (35.2%)	316 (33.5%)	
Summer	188 (24.6%)	41 (23.0%)	229 (24.3%)	
Fall	145 (18.9%)	37 (20.6%)	181 (19.2%)	
Distance to hospital (miles): median (Q1, Q3) *	5.0 (2.4, 9.4)	4.4 (2.3, 7.6)	5.0 (2.4, 9.2)	0.95
Does the child have a primary medical doctor?: yes	719 (93.9%)	169 (95.4%)	888 (94.1%)	0.29
Presence of vomiting at presentation: yes	583 (76.2%)	134 (75.4%)	717 (76.0%)	0.90
Duration of vomiting before randomization (hours): median (Q1, Q3)	27.4 (3.5, 61.5)	29.0 (1.7, 73.6)	27.8 (3.2, 63.2)	0.25
Number of vomiting episodes in the 24 hours before randomization: median (Q1, Q3)	2.0 (0.0, 5.0)	2.0 (0.0, 5.0)	2.0 (0.0, 5.0)	0.75
Duration of diarrhea before randomization (hours): median (Q1, Q3)	53.5 (29.2, 81.6)	51.9 (28.2, 80.8)	53.2 (29.0, 81.4)	0.82

	Did subject complete all 10 doses			
	Yes (N = 766) (81.2%)	**No (N = 177) (18.8%)**	**Overall (N = 943)**	***P* value**
Number of diarrheal episodes in the 24 hours before randomization: median (Q1, Q3)	6.0 (4.0, 9.0)	5.0 (4.0, 8.0)	6.0 (4.0, 9.0)	0.41
Baseline MVS score: median (Q1, Q3)	12.0 (10.0, 14.0)	11.0 (9.0, 13.0)	12.0 (10.0, 14.0)	0.43
What was the highest temperature? (celsius): median (Q1, Q3)	39.4 (38.9, 40.0)	39.4 (38.5, 40.0)	39.4 (38.9, 40.0)	0.23
Prior ED visit for the current illness: yes	30 (4.0%)	8 (4.3%)	38 (4.0%)	0.70
Hospitalization at index visit: yes	33 (4.4%)	11 (6.0%)	44 (4.7%)	0.16
Hospitalization within 7 days of discharge: yes	8 (1.1%)	8 (4.3%)	16 (1.7%)	0.01
Does your child go to daycare?: yes	295 (38.5%)	58 (32.8%)	353 (37.5%)	0.15
Were any IV fluids administered during ED visit?: yes	126 (16.4%)	39 (22.2%)	165 (17.5%)	0.02
Was the child given Ondansetron during the ED visit?: yes	345 (45.1%)	82 (46.1%)	427 (45.3%)	0.96
Was the child given antibiotics during the ED visit?: yes	35 (4.5%)	8 (4.2%)	42 (4.5%)	0.82
Return visit consistent with gastroenteritis within 14 days: yes	109 (14.2%)	28 (15.8%)	137 (14.5%)	0.47
Return ED visit consistent with gastroenteritis within 14 days: yes	54 (7.1%)	15 (8.2%)	69 (7.3%)	0.70
IV rehydration in the ED within 7 days of discharge?: yes	18 (2.3%)	7 (3.8%)	25 (2.6%)	0.27
Ondansetron received at home?: yes	72 (9.4%)	20 (11.2%)	92 (9.7%)	0.21
Maximum number of vomit episodes in 24 hours: median (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.01
Duration of vomiting after randomization: median (Q1, Q3)	0.0 (0.0, 2.1)	0.0 (0.0, 12.1)	0.0 (0.0, 3.7)	0.03
Maximum number of diarrhea stools in 24 hours: median (Q1, Q3)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	0.63
Duration of diarrhea after randomization: median (Q1, Q3)	51.7 (23.2, 88.4)	46.0 (15.6, 80.9)	50.3 (22.3, 87.6)	1.00
Side effects reported within 5 days: yes	212 (27.7%)	49 (27.5%)	261 (27.7%)	0.79
Dehydration Score: mean (SD)	0.6 (1.16)	0.8 (1.47)	0.6 (1.23)	<.01

ED = emergency department; IV = intravenous; SD = standard deviation.

*All distances to hospital greater than 90 miles have been trimmed to 90 miles. *P* values come from individual logistic regression models using the listed variable, with adherence (yes/no) as the outcome, adjusting for site and duration of symptoms.

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TABLE 2.

Multivariable effect of predictors on nonadherence

Variable	Odds ratio (95% CI)	*P* value
Age (increase of 1 year)	1.19 (1.00–1.43)	0.05
Base MVS Score (increase of 1 point)	0.87 (0.80–0.95)	<0.01
Vomiting duration at baseline (increase of 24 hours of vomiting)	1.23 (1.05–1.45)	0.01
Dehydration score (increase of 1 point)	1.23 (1.07–1.42)	<0.01
Hospitalization within 7 days of discharge	4.16 (1.21–14.30)	0.02

Final model determined using backwards elimination, adjusting for site and symptom duration. Candidate predictors were based off predetermined factors of interest and all other variables with univariate *P* values of <0.2. The cut-off probability for remaining in the model was <0.10. The following were considered as a priori candidate predictors: patient has a primary doctor, baseline MVS, baseline vomit duration, baseline number of vomit episodes in 24 hours before enrollment, baseline diarrhea duration, baseline number of diarrhea episodes in 24 hours before enrollment, Ondansetron received in the emergency department (ED), treatment arm, return healthcare visit, return ED visit, intravenous (IV) fluids in subsequent 7 days, Ondansetron prescribed, maximum number of diarrhea episodes after enrollment, and diarrhea duration after enrollment. The following were considered as candidate predictors based on a uniavariate *P* value of <0.2: age, hospitalization at index visit, subsequent hospitalization within 7 days, attends daycare, IV fluids at index visit, maximum number of vomit episodes after enrollment, vomit duration after enrollment, and dehydration score.

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