

# Adjunctive Pharmacotherapy for the Treatment of Diarrhea in Infants and Children: A Noninferiority Trial

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## Abstract

**Study Objective:** To assess the relative efficacy of adjunctive oral therapies in the treatment of mild to moderate uncomplicated diarrhea in infants and children.

**Design:** Randomized, Single-Blind, placebo controlled, seasonally balanced.

**Setting:** Pediatric ward, Regional tertiary-level care, general medical hospital in Santa Ana, El Salvador, Central America.

**Patients:** 106 indigent infants and children with acute onset of mild to moderate uncomplicated diarrheal illness

**Interventions:** Symptomatic and supportive peroral administration adjunctive oral therapies and rehydration.

**Measurements and Main Results:** An oral, liquid pediatric multi-vitamin formulation containing Vitamin A outperformed placebo and performed as well or better than bismuth subsalicylate in decreasing the total number of bowel movements, diminishing total stool weight, and limiting the duration of the study.

**Conclusion:** An over-the-counter liquid, pediatric multi-vitamin formulation containing Vitamin A appears to demonstrate efficacy in ameliorating the signs and symptoms of mild to moderate, uncomplicated diarrheal illness in infants and children.

**Key Descriptors:** Diarrhea, Vitamin A, Infants and Children

**Running Head:** Adjunctive pharmacotherapy for Diarrheal Illness.

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## Introduction

Worldwide, diarrhea remains one of the most common illnesses among children.<sup>1,2</sup> Uncontrolled diarrhea often associated with malnutrition causes or contributes to the death of over three million infants and children in developing nations each year. Pharmacotherapy for acute diarrheal illness is usually non-specific, adjunctive, and not cost-effective as the limited resources available in the countries hardest hit are often grossly inadequate to provide prevention or effective treatments other than rehydration. Worldwide, no clear consensus concerning the value of adjunctive therapies has been reached.<sup>3,4</sup> In this preliminary study, we report the results of a placebo controlled trial of several commonly available pharmacological interventions.

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## Methods

**SUBJECT SELECTION:** 106 infants and children from twelve months to five years of age with uncomplicated, mild to moderate diarrheal illness and minimal dehydration were consented and randomized into the IRB approved protocol. Ninety-six patients completed the study. Each study participant received standardized oral rehydration therapy in addition to any other interventions. Exclusion criteria included fever > 103.5oF and/or bloody diarrhea. Fifty-one of the study subjects were female; all were demographically matched. (See Table 1.)

**ENTRY CRITERIA:** Patients were deemed appropriate to participate in the trial if each subject had a history of not less than three watery stools or poorly formed stools within 24 hours of the initial evaluation and had not received antibiotics and/or opioid anti-diarrheals.

**INTERVENTIONS and TREATMENT SCHEDULES:** Initially, each subject was observed for a period of not less than six hours. Concurrent with the first observed stool, patients were randomly assigned to one of six treatment groups, each of which consigned the participant to treatment with one of four presumably active medications, a placebo, or oral rehydration. The placebo chosen was a commercially available, OTC liquid pediatric multivitamin formulation.

Concurrent with stool #1, the first peroral dose of: oral glucose-electrolyte rehydration solution(OGE) (Treatment 1), liquid kaolin-pectin suspension (Treatment 2), bismuth subsalicylate (Treatment 3), a proprietary, phyto-extract solution(Treatment 4), loperamide liquid (Treatment 5), or a pediatric multivitamin liquid (Treatment 6) was administered. Dosing was based on volume of medication per kilogram (kg) of total body weight. In addition to treatment and placebo, all subjects received oral rehydration with the OGE solution in an amount of 60 mL every 8 hours. Once initiated, therapy was continued until a significant therapeutic end-point was achieved or the study was terminated because of clinical deterioration of the patient or by request the physician and/or responsible adult family member-guardian. By consensus, a potentially significant therapeutic end-point was defined when an interval of  $8 \pm 0.5$  hours had elapsed during which no stools(BM's) were documented.

**OUTCOME MEASURES:** A priori, five outcome measures were defined: total number of bowel movements (TBM's); total weight of stool accumulated during the study duration (TSW); the ratio of total stool weight to total body

**Table I**  
**Characteristics of the Study Groups**

Characteristic	Placebo	Kaolin-pectin	Bismuth Subsalicylate	Phyto-Extract	Loperamide	Pediatric Multivitamin Liquid *
	N = 16	N = 17	N = 18	N = 16	N = 14	N = 15
Age (mo)	13.8± 9.6	14.3±9.7	10.2±4.7	11.68±5.4	12.07±6.7	11.73±6.12
Weight (Kg)	9.2±2.2	9.2±2.1	8.6±1.5	9.4±2.5	9.2±1.7	8.8±1.4
Duration of Diarrhea before Admission (Days)	1.21±0.8	3.3±3.8	2.8±2.6	3.4±5.6	2.9±2.8	3.3±4.1

\* Contents per 1 mL: Vitamin A 1500 IU, Vitamin D 400 IU, Vitamin E 5 IU, B1 0.5mg, B2 0.6mg, B3 8mg, B6 0.4mg, B12 2 mcg, C 35mg.

weight(TSW/TBW); the total number of doses of each treatment administered; and the total study duration or length of time needed to achieve a stool-free interval of 8 +/- 0.5 hours. The weight of each stool(wet weight) was calculated as the difference in weight between the dry weight of a standardized, commercially available 'brand name' diaper and the total weight of the diaper containing a single stool.

ANALYSIS OF DATA: A parametric statistical analysis was chosen based on the results of D'Agostino's Robust Test for assessing the 'Normality' of underlying distributions. Analysis of variance (ANOVA) and the paired-t statistic were used to test for the significance of differences among means and variances. A two-variable linear regression was used to assess strength of associations. Statistical significance could be assigned when P values were < 0.05 (two-tailed), and all means were expressed as ± 1 standard deviation (± 1 SD) unless otherwise stated.

### Results

When each outcome measure was evaluated at the termination of the study, clinically significant trends, but no statistically significant differences, were observed in response to the adjunctive therapies among the treatment groups. It was reasonable to infer that one of the treatments, Treatment 6, the pediatric multivitamin liquid formulation had performed as well as and was noninferior in performance<sup>5</sup> to bismuth-subsalicylate and the OGE rehydration solution on three of the five outcome measures: the total number of bowel movements (TBM's), total stool weight (TSW), and the total duration of the study.

Of special significance was the fact that these potentially

clinically important, but statistically non-significant results were attributable to Treatment 6, the liquid pediatric multivitamin placebo containing Vitamin A, and that treatment 6 had performed better than the OGE rehydration solution and as well as, or better than, bismuth-subsalicylate,<sup>5</sup> the 'benchmark treatment' adjunctive therapy which has been shown to demonstrate efficacy in the treatment of diarrheal illness.<sup>3,6</sup>

### Discussion

In the present study, we observed potentially clinically important trends in the reduction of total stool weight, total number of bowel movements, and in the duration of the study in patients receiving a pediatric multivitamin liquid originally included as a second placebo. Our results suggest the probable effectiveness of the pediatric multivitamin formulation in limiting the duration and ameliorating acute, non specific diarrheal illness. We attribute, arguably, the observed salutary effect of the multivitamin formulation to its Vitamin A content. In retrospect, the apparent therapeutic benefits of Vitamin A in the treatment of diarrhea were not completely unanticipated. Nevertheless, the magnitude and extent of the treatment effect that we observed was not expected.

Severe diarrhea is a potentially pathogenic exaggeration of the normal physiology of gastrointestinal secretion,<sup>7</sup> while mild to moderate diarrhea can be thought of as a potentially beneficial 'house-keeping' response to toxins, non-self immunogens/antigens, and a plethora of molecules and diarrheal incitants which damage intestinal mucosa, either thru direct cytotoxicity and/or via interference with the energy dependent processes that maintain normal transluminal

intestinal fluid and electrolyte gradients.<sup>8,9</sup> For the purposes of this discussion, and based on our experience, vitamin A, a major component, among the several vitamin and mineral constituents of the liquid pediatric multivitamin formulation that we chose to include as a placebo, is, arguably, the most likely active ingredient to which a therapeutic benefit and the amelioration of mild to moderate uncomplicated diarrhea can be attributed. Vitamin A, or retinol, is critical to maintaining normal epithelial function<sup>10</sup> and an intact immune system in man and animals.<sup>11</sup> Conversely, humans and animals chronically deprived of vitamin A, as suspected to have existed in our indigent, historically poorly nourished/undernourished patients, suffer from deprivation of this essential vitamin by exhibiting systemic diseases which are often associated with diarrhea most probably characterized by, and attributable to epithelial (gastrointestinal mucosal) dysfunction<sup>12,15,16</sup> and the attendant massive fluid and electrolyte loss. Barreto et al,<sup>13</sup> Bhandari et al,<sup>14</sup> and Long et al<sup>15</sup> have all demonstrated that Vitamin A supplementation appears to have a salutary effect that ameliorates diarrhea illness in infants and children in developing nations, eg., El Salvador, who often suffer from undernutrition.

Other than Vitamin A, none of the other constituents of the multi-vitamin formulation or the other adjunctive treatments evaluated in this study have been shown to have mechanisms of action which influence or mediate energy-dependent, physiological processes in the gut that predictably or reliably modify the clinical course of diarrheal illness.

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### Conclusion

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Our data and results support the inference that in this limited study, Vitamin A, as a component of a an OTC pediatric multivitamin formulation, might be particularly efficacious when used as adjunctive, nonspecific pharmacotherapy in the treatment of diarrhea in indigent, presumably nutritionally deprived infants and children similar to those who comprised our study population. The Authors consider the results and inferences drawn from this study to be provocative and of sufficient value to stimulate the requisite interest and research expertise needed to conduct larger, more rigorously designed trials of the efficacy of Vitamin A as a single therapy, or as a component of a multivitamin formulation, in the treatment of diarrheal illness in Infants and children.

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