Optimizing Management of Paediatric Diarrhoeal Disease in Botswana: A Pilot, Factorial, Randomized, Placebo-Controlled Trial of Rapid Enteric Diagnostics and Probiotic Therapy

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Introduction

Diarrhoeal disease is the second-leading cause of death for children under the age of five years (1). Diarrhoea also actively facilitates the development of severe acute malnutrition, itself responsible for much child mortality and disability. The duration of child diarrhoeal ilness has been shown to correlate well with the development of stunting (height-for-age [HAZ] less than 2 SD below the mean) at the age of two (2). Stunting, for its part, has been linked to cognitive maldevelopment (3) and has been found to be the best predictor of decreased adult human capital (4). Strategies to mitigate the effects of diarrhoeal disease are sorely needed.

Current World Health Organization (WHO) guidelines recommend giving rehydration solutions and zinc therapy promptly for supportive treatment of acute gastroenteritis regardless of aetiology (5). If there is blood in the stool, WHO also recommends presuming *Shigella* is causing the infection and providing appropriate antimicrobials (5). Unfortunately, the presence of blood in the stool is neither sensitive nor specific for the detection of treatable enteric pathogens; furthermore, infections with selected pathogens (*Campylobacter, Shigella,* and enterotoxigenic *E. coli* [ETEC]) have been shown to be associated with mortality, with this estimate not significantly modified by the occurrence of bloody stools (6).

Numerous systematic reviews have documented that probiotic preparations appear to diminish the duration and severity of acute gastroenteritis; however, there are few data to date examining their effect on bacterial enteric disease.

The objective of this study was to determine if rapid diagnostic testing (permitting timely antimicrobial therapy) and/or treatment with *Lactobacillus reuteri* DSM 17938 would be associated with improved outcomes in children admitted to hospital with severe acute gastroenteritis in Botswana.

Methods

- A pilot, randomized, factorial, randomized, placebo-controlled trial
- **Inclusion:** Children aged 2-60 mos. hospitalized for acute gastroenteritis (3 stools < 24 h)
- **Exclusion:** Bloody stools, diarrhoea > 14 d, chronic conditions (ie. IBD, CF, malignancy), suspected sepsis/UTI/pneumonia/meningitis requiring antimicrobials, an epidemiologic link to an individual with a defined enteric infection, or children transferred in on antibiotics
- Sites: Princess Marina Hospital (Gaborone), Bamalete Lutheran Hospital (Ramotswa), Scottish Livingstone Hospital (Molepolole)
- all participants received fluid rehydration and zinc therapy, as per WHO standard

Participants randomized to 4 groups:

1. rapid enteric testing + treatment (if indicated) + *L. reuteri* DSM 17938
2. rapid enteric testing + treatment (if indicated) + placebo
3. delayed testing + *L. reuteri* DSM 17938
4. delayed testing + placebo

- Rectal flocked swabs collected at time of enrolment; rapid testing results back same-day
  - two multiplex PCR assays on ABI 7500
  - those with stools positive for *Campylobacter* or *Shigella* or ETEC given azithromycin x 3 d
  - those with stools positive for *Cryptosporidium* given nitazoxanide x 3 d
- Probiotic/placebo oil emulsions, identical bottles
  - *L. reuteri* dose $5x10^8$ cfu/day x 60 days
- Primary outcome: HAZ at 60 days adjusted for baseline height
- Secondary outcomes:
  - recurrence of diarrhoea in 60 days
  - standardized weight at 60 days (adjusted)
  - environmental enteropathy score at 60 days

Results

Table 1. Baseline participant characteristics.

	Rapid + *L. reuteri*	Rapid + placebo	Delayed + *L. reuteri*	Delayed + placebo
# participants	20	18	14	21
mean age (y)	0.99	1.06	1.08	1.20
% female	30	56	57	48
baseline HAZ	-0.98	-1.37	-0.52	-0.74
days of diarrhoea	2.6	2.1	2.1	3.4
days of vomiting	7.2	2.3	2.3	2.6
%ORS before admission	50	78	79	81
% febrile	70	89	79	62
% IV fluids	85	83	79	100

Table 2. Enteric pathogens detected.

	Rapid testing (n=38)	Delayed testing (n=35)
Campylobacter	10 (25%)	14 (47%)
Shigella	8 (20%)	6 (21%)
ETEC	4 (13%)	4 (13%)
Cryptosporidium	1 (2.5%)	4 (12%)
Total treatable	19 (48%)	18 (55%)

Table 3. Difference in HAZ adjusted for baseline.

group	difference in HAZ @ 60 d adjusted for baseline (95% CI)	p
Delayed testing + placebo	(ref)	
Rapid testing + placebo	+ 0.28 (-0.26 to 0.81)	0.31
Delayed testing + *L. reuteri*	+ 0.67 (0.08 to 1.27)	0.03
Rapid testing + *L. reuteri*	+ 0.63 (0.12 to 1.13)	0.02

Table 4. Recurrence of diarrhoea in 60-d followup.

group	OR of recurrence of diarrhoea by 60 days (95% CI)	p
Delayed testing + placebo	(ref)	
Rapid testing + placebo	0.45 (0.12 to 1.79)	0.26
Delayed testing + *L. reuteri*	0.11 (0.01 to 1.05)	0.06
Rapid testing + *L. reuteri*	0.07 (0.01 to 0.61)	0.02

Discussion

The results of this randomized pilot trial confirm our hypothesis that rapid test-and-treat algorithms and probiotic therapy offer real promise for the treatment of severe gastroenteritis in the southern African context. We have demonstrated that the integration of rapid molecular testing into routine care, made possible by the use of rectal flocked swabs, is feasible in resource-limited settings.

The combination of rapid diagnostic testing and *L. reuteri* DSM 17938 treatment was associated with both statistically significant increases in standardized height (adjusted for baseline height) and statistically significant decreases in recurrent diarrhoea. It is very possible that the estimates in treatment effect observed in this small study were exaggerated due to to chance; one should also remember that there were baseline differences between arms. However, we believe that further exploration of these interventions in an adequately-powered multicentre trial is warranted.

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