

# Management of acute diarrhoea with low osmolarity oral rehydration solutions and *Lactobacillus* strain GG

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## Abstract

**Two hypotonic oral rehydration solutions with osmolarities of 224 mosmol/l (Na<sup>+</sup> 60 mmol/l, glucose 84 mmol/l) and 204 mosmol/l (Na<sup>+</sup> 60 mmol/l, glucose 64 mmol/l), respectively, and oral treatment with *Lactobacillus* GG were evaluated in a double blind trial in children aged 6-36 months hospitalised for acute diarrhoea. Early administration of *Lactobacillus* GG at the start of oral rehydration resulted in the shortest duration of diarrhoea, best weight gain, and fastest correction of acidosis. A reduced osmolarity oral rehydration solution (224 mosmol/l) combined with early administration of *Lactobacillus* GG is an effective treatment for acute diarrhoea in young children; further reduction of osmolarity may not be beneficial.**

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Comprehensive management of acute diarrhoea in children consists of oral rehydration, appropriate nutritional treatment, and various auxiliary treatments aimed at shortening the diarrhoeal episode.<sup>1-5</sup> All these components of treatment may contribute to correction of dehydration, better weight gain, and the reduction of both watery stools and the duration of diarrhoea.

Hypotonic oral rehydration solution with an osmolarity of 224 mosmol/l is effective in reducing stool output, as compared with isotonic oral rehydration solution.<sup>6,7</sup> Studies in experimental animals and in human volunteers have suggested that the optimal osmolarity for absorption of water from oral rehydration solutions might be in the range of 200-250 mosmol/l.<sup>8-13</sup> Accordingly, our study explored the lower limit of this range, to see whether a solution with osmolarity of 204 mosmol/l might offer any advantage over 224 mosmol/l, the osmolarity of hypotonic oral rehydration solutions investigated in our previous studies.<sup>6,7</sup>

*Lactobacillus* strain GG, ATCC 53103, has been shown to shorten the duration of acute diarrhoea,<sup>4,5,14,15</sup> and to reduce the duration of rotavirus excretion in diarrhoea<sup>15</sup>; therefore, it can be regarded as a promising auxiliary treatment of acute diarrhoea in children. We examined whether immediate administration of *Lactobacillus* GG at the time of initiation of oral

rehydration treatment results in further benefit compared with its administration after initial oral rehydration, at the time of resumed feeding.

## Patients and methods

The study was carried out at the Aurora Hospital, Helsinki. The study protocol was approved by the ethics review committee of the Health Care Centre of Helsinki. Parents were given verbal and written information about the study before a written witnessed consent was obtained for the enrolment of their child in the study.

Altogether, 123 children aged 6-36 months, suffering from acute diarrhoea (duration less than seven days) and needing hospitalisation, were included in the study. Rotavirus was detected in the stools of 113 (92%) of the children. Patients with a serum sodium concentration above 155 or below 130 mmol/l were excluded (only one patient). Furthermore, five patients who were enrolled but required intravenous rehydration were excluded from analysis.

Alternate children received an oral rehydration solution with either an osmolarity of 224 mosmol/l (hypotonic oral rehydration solution) or 204 mosmol/l (ultrahypotonic oral rehydration solution). Table 1 gives the molar compositions of the two solutions. The solutions were prepared by the central pharmacy of Helsinki City Hospitals, and supplied as a dry powder, which was dissolved in 500 ml of water on the ward. The sachets containing the powder and the two solutions after reconstitution were identical in appearance. The oral rehydration solutions were labelled as solutions I and II. Only the pharmacy personnel knew the code for the solutions during the study.

In addition to the oral rehydration solution treatment, patients were randomised to receive *Lactobacillus* GG or placebo powder twice a day during the hospital stay. The *Lactobacillus* GG was provided in 1.25 g freeze dried doses in small plastic bags containing  $5 \times 10^9$  colony forming units/dose and stored at  $-18^\circ\text{C}$ . The placebo powder was microcrystalline cellulose

Table 1 Composition of the hypotonic and ultrahypotonic oral rehydration solution used in the study

	Hypotonic	Ultrahypotonic
Sodium (mmol/l)	60	60
Potassium (mmol/l)	20	20
Chloride (mmol/l)	50	50
Glucose (mmol/l)	84	64
Citrate (mmol/l)	10	10
Total osmolarity (mosmol/l)	224	204

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Table 2 Patient groups

Group	First dose during initial rehydration	Following doses during hospital stay
1	Sachet A	Sachet A
2	Sachet A	Sachet B
3	Sachet B	Sachet A
4	Sachet B	Sachet B

(Ph. Eur. 2nd ed. II). The *Lactobacillus* GG and placebo bags and powders were identical in appearance. The freeze dried powders were mixed with 5 ml of water and given by spoon or a nasogastric tube. These powder sachets were packed and supplied by Valio Ltd (Helsinki, Finland). Sachets were labelled with codes A and B: A contained *Lactobacillus* GG and B contained placebo. Patients were randomised to one of four different treatment groups (table 2).

In this way, patients received either one early *Lactobacillus* GG dose only, *Lactobacillus* GG twice a day throughout the hospital stay, *Lactobacillus* GG during the maintenance phase only, or placebo only.

The oral rehydration solution was prescribed according to the patient's degree of dehydration. This was assessed by the physician in the emergency ward by calculating the acute weight loss against pre-morbid weight or according to clinical signs of dehydration. It was recommended that four thirds of the estimated fluid deficit was given during the first six to eight hours. If necessary, the solution was given through a nasogastric drip. After the first six to eight hours of rehydration, the children were given additional oral rehydration solution to the volume of the diarrhoeal stools and vomits lost, estimated by the physician and nurses in the ward. Normal feeding for age was resumed immediately after the six to eight hour rehydration period. Fermented milk products

Table 3 Characteristics of the patients on admission according to oral rehydration solution (ORS) given

	Hypotonic ORS (n = 59)	Ultrahypotonic ORS (n = 64)
<i>Admission</i>		
Patients (%) with rotavirus	56 (95%)	57 (89%)
Age (months)	17.0 (14.9 to 18.3)	18.0 (16.2 to 20.6)
Duration of diarrhoea before admission (hours)	66 (59 to 74)	63 (56 to 71)
Acute weight loss (g)	463 (431 to 496)	462 (417 to 506)
Admission weight (kg)	10.1 (9.7 to 10.5)	10.6 (10.0 to 11.2)
Blood sodium concentration (mmol/l)	137 (136 to 138)	137 (136 to 137)
Blood potassium concentration (mmol/l)	4.1 (4.0 to 4.3)	4.2 (4.1 to 4.3)
Blood base excess (mmol/l)	-7.6 (-8.6, to 6.7)	-6.7 (-7.6, to 5.8)
<i>Bacteriotherapy</i>		
Patients (%) with early LGG treatment	31 (53%)	30 (47%)
<i>Rehydration treatment</i>		
Initial rehydration (ml)	631 (587 to 675)	614 (576 to 652)
Total consumption of ORS (ml)	1388 (1211 to 1564)	1356 (1216 to 1495)

Values are mean (95% confidence intervals) except where stated.

Differences between the groups were not significant.

LGG, *Lactobacillus* strain GG.

Table 4 Effect of type of oral rehydration solution (ORS) and early dose of *Lactobacillus* strain GG (LGG) on duration of diarrhoea in the hospital (hours)

	Hypotonic ORS	Ultrahypotonic ORS
Early dose of LGG	17.7 (12.2 to 25.6)	29.5 (23.2 to 37.7)
No early dose of LGG	30.4 (23.6 to 39.3)	30.4 (24.8 to 37.2)

Values are mean (95% confidence intervals).

ANOVA: effect of ORS,  $F = 3.79$ ,  $p = 0.05$ ; effect of LGG,  $F = 4.78$ ,  $p = 0.03$ ; interaction,  $F = 3.88$ ,  $p = 0.05$ .

were excluded from the diet to prevent interference in the dietary intervention.

The exact amount of oral rehydration solution consumed was recorded by the ward nurses. They also recorded the number and quality of the stools passed by the children (characterised as watery, loose, or solid) and vomiting episodes. Weight was measured on admission, after initial rehydration, and daily thereafter during the hospital stay. Blood sodium and potassium concentrations and acid-base balance were determined on admission and daily thereafter. A stool sample was taken during the hospital stay for the detection of rotavirus, using an enzyme immunoassay (Rotazyme; Dako, Glostrup, Denmark).

The analysis of variance (including two factor ANOVA and ANOVA for repeated measures) was used in statistical comparisons. Natural logarithmic transformation was used when appropriate because of skewed distribution.

## Results

### ORAL REHYDRATION

Of the 123 patients, 59 received hypotonic oral rehydration solution and 64 received ultrahypotonic oral rehydration solution. The two oral rehydration solution groups did not differ for the presence of rotavirus. The number of patients receiving early *Lactobacillus* GG treatment was similar in both oral rehydration solution groups (table 3). The age of the patients and the clinical picture on admission were comparable in both oral rehydration solution groups (table 3). The consumption of oral rehydration solution was similar in both groups (table 3). The blood sodium and potassium concentrations remained similar in both oral rehydration solution groups during the whole hospital stay (ANOVA for repeated measures).

### BACTERIOTHERAPY

Of the 123 patients, 61 received early *Lactobacillus* GG treatment during rehydration. Of these, 28 received one single dose and 33 continued to receive *Lactobacillus* GG twice a day during the whole hospital stay. Of the remaining 62 patients, 32 received an initial dose of placebo, and thereafter *Lactobacillus* GG, and 30 received only placebo throughout the hospital stay.

### OUTCOME OF PATIENTS

Both early *Lactobacillus* GG treatment and hypotonic oral rehydration solution had an independent effect on the duration of diarrhoea (table 4). ANOVA demonstrated that there was a significant interaction between the two interventions. The mean duration of diarrhoea in the subgroup receiving early *Lactobacillus* GG together with the hypotonic oral rehydration solutions was 17.7 hours (95% CI, 12.2 to 25.6), significantly shorter than the other subgroups (table 4). There was no difference between the groups receiving early or late *Lactobacillus* GG with either type of oral rehydration solution in the number of stools passed in hospital (which was between seven and eight in all groups).

The best weight gain during rehydration was achieved in the group receiving hypotonic oral rehydration solution and early *Lactobacillus* GG treatment, in which the mean weight gain was 262 g (95% CI, 170 to 355). In the group receiving the ultrahypotonic oral rehydration solution without early *Lactobacillus* GG, the mean weight gain was 127 g (95% CI, 27 to 227). The hypotonic oral rehydration solution rather than early *Lactobacillus* GG treatment was responsible for weight gain during rehydration ( $F = 3.76$ ,  $p = 0.06$ ;  $F = 1.11$ ,  $p = 0.29$ , respectively); no interaction between the two interventions was seen in this respect.

The best recovery from acidosis was also seen in the group receiving the hypotonic oral rehydration solution and early *Lactobacillus* GG, but the differences were not significant. The mean base excess after rehydration was  $-2.8$  mmol/l in this group, higher than in any other treatment group.

### Discussion

Our previous studies showed that a hypotonic oral rehydration solution with an osmolarity of 224 mosmol/l performs better than an isotonic oral rehydration solution.<sup>6,7</sup> In the present study, we wanted to find out whether a further reduction in osmolarity to 204 mosmol/l and of glucose content to 64 mmol/l would improve the rehydrating properties of the oral rehydration solution still further. Both hypotonic oral rehydration solutions were effective for treatment of dehydration. However, there was a small difference in favour of the solution with an osmolarity of 224 mosmol/l, which was better in correcting weight loss and acidosis, and was associated with a slightly shorter duration of diarrhoea. Probably, both solutions contained a sufficiently low concentration of glucose not to provoke osmotic diarrhoea. The oral rehydration solution with the higher glucose content might have resulted in faster recovery from acidosis and cessation of diarrhoea because of a greater glucose enhanced sodium and water uptake in the small intestine.

Using healthy rats, Wapnir *et al* compared several oral rehydration solutions with osmolarities from 155 to 330 mosmol/l and different sodium and glucose contents. The maximum water absorption was seen for solutions with very low osmolarity (155–220 mosmol/l) and glucose content (30 mmol/l). However, a slight increase of the glucose content (45–111 mmol/l) resulted in higher sodium uptake, although the sodium concentrations stayed constant.<sup>12</sup> Farthing recommended that the sodium concentration should be  $\sim 60$  mmol/l and the glucose content between 50 and 100 mmol/l to ensure optimal water and sodium absorption, based on studies with cholera toxin treated rat small intestine and rotavirus infected neonatal rats.<sup>9</sup>

Clinical studies of children with diarrhoea have compared various hypotonic solutions with the oral rehydration solution recommended by the WHO (osmolarity 311 mosmol/l, sodium 90 mmol/l, glucose 111 mmol/l). Solutions with osmolarities of 249 mosmol/l (sodium 60 mmol/l, glucose 89 mmol/l), 224 mosmol/l (sodium 60 mmol/l,

glucose 84 mmol/l), and 210 mosmol/l (sodium 60 mmol/l, glucose 75 mmol/l) have been investigated.<sup>16–18</sup> In all studies, the hypotonic solutions performed better than standard oral rehydration solutions, although in a study in Bangladesh the hypotonic solution (249 mosmol/l) was beneficial only in rotavirus negative patients.<sup>16</sup> In contrast, in our previous study a hypotonic oral rehydration solution with osmolarity of 224 mosmol/l performed well in rotavirus positive patients,<sup>7</sup> a finding confirmed in the present study.

As seen in earlier studies in Tampere and elsewhere,<sup>4,5,14,15</sup> *Lactobacillus* GG significantly shortened the duration of diarrhoea. Guarino *et al* found that administration of *Lactobacillus* GG also significantly shortened the excretion of rotavirus in acute diarrhoea.<sup>15</sup> Our study shows that to reach maximal effect, *Lactobacillus* GG should be given as early as possible. The results suggest that a single early dose of *Lactobacillus* GG might be sufficient, because further doses during the maintenance phase did not improve the outcome. Theoretically, a single dose of *Lactobacillus* GG could result in sufficient colonisation, which might be maintained for up to seven days after ingestion.<sup>19</sup>

Recently, it has been suggested that rotavirus infection gives rise to a biphasic diarrhoeal illness, first causing an osmotic diarrhoea and later overgrowth of urease producing bacteria.<sup>20</sup> Rotavirus infection causes patchy lesions in the small intestine mucosa.<sup>21</sup> This leads to reduced absorptive properties and malabsorption of carbohydrate,<sup>22</sup> and to osmotic diarrhoea, which turns the colonic contents acidic.<sup>23</sup> The acidic stools convert ammonia to ammonium ions, which are poorly absorbed from the colon.<sup>24</sup> Unabsorbed ammonium ions provide nitrogen to many enteric bacteria, including urease producing bacteria.<sup>25</sup> Overgrowth of urease producing bacteria might predispose to further mucosal damage, initiated by rotavirus infection.<sup>25,26</sup> Following this hypothesis, an intervention that reduces ammonia content or bacterial overgrowth in the intestine could decrease the severity of rotavirus infection. Oral administration of lactobacilli has been identified as such an intervention.<sup>20</sup> In addition, hypotonic oral rehydration solutions prevent osmotic diarrhoea and acidification of the stools,<sup>7</sup> which might also reduce bacterial overgrowth and prevent the second phase of rotavirus infection. This could explain the positive interaction between the *Lactobacillus* GG treatment and the hypotonic oral rehydration solution.

Based on these findings, we conclude that both *Lactobacillus* GG and hypotonic oral rehydration solutions are safe and effective treatments of acute diarrhoea and seem to have a positive interaction. For optimal effect, we suggest that *Lactobacillus* GG should be given with the oral rehydration solution during initial rehydration.

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