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Rice-ORS versus Glucose-ORS in Management of Severe Cholera Due to *Vibrio cholerae* O139 Bengal: A Randomized, Controlled Clinical Trial

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ABSTRACT

This study examined the comparative efficacies of rice-based oral rehydration solution (R-ORS) and glucose-based oral rehydration solution (G-ORS) in the management of severe cholera due to *Vibrio cholerae* O139 Bengal that causes epidemic cholera in many developing countries. Stool culture-proved adult male patients with severe cholera due to *V. cholerae* O139 Bengal were randomly assigned in a 1:1 ratio to receive either R-ORS or G-ORS after their initial rehydration with intravenous (i.v.) fluid and subsequently four hours of observation. They also received the usual hospital diet and tetracycline capsules (500 mg 6 hourly for three days) immediately after their enrollment in the study. The primary outcomes for observation were stool output during the first 24 hours after intervention and treatment failure as measured by the incidence of re-institution of i.v. fluid after initiation of trial therapy and duration of diarrhoea. Of 113 patients finally included in the study, 57 received R-ORS and 56 G-ORS. The admission characteristics of the two treatment groups were comparable. No significant differences in the first 24 hours of median (inter-quartile range) stool output [179 (67-206) g/kg in R-ORS group vs 193 (80-237) g/kg in G-ORS group; p=0.52], incidences of unscheduled i.v. fluid requirement [21% (12/57) in R-ORS group vs 25% (14/56) in G-ORS group; p=0.78], and median (inter-quartile range) duration of diarrhoea [32 (24-48) hours in R-ORS group vs 32 (24-56) hours in G-ORS group; p=0.64] were observed. It is concluded that rice-based ORS is effective but not superior to standard glucose-based ORS in the management of adult males with severe cholera due to *V. cholerae* O139 Bengal.

***Key words*:** Oral rehydration therapy; Oral rehydration solution; Rice; Dehydration; Cholera; *Vibrio cholerae*; Clinical trials; Randomized controlled trials; Bangladesh

INTRODUCTION

During 1992-1993, outbreaks of cholera-like diarrhoea were reported from southern India and Bangladesh (1-4). The illness was not caused by the most common *Vibrio cholerae* O1 but by another strain of *V. cholerae* (5-6). The pathogen was later confirmed as a new serovar of *V. cholerae* designated as *V. cholerae* O139 synonym Bengal (7,8). Its clinical presentation and immunobiological characteristics are similar to those of cholera caused by *V. cholerae* O1 (9-11).

Although oral rehydration solution (ORS) has been shown to be useful in the treatment of all types of watery diarrhoea, including cholera due to *V. cholerae* O1, its role has not been evaluated in cholera caused by *V. cholerae* O139. The World Health Organization (WHO) recommends glucose-based ORS (G-ORS) for oral rehydration therapy (ORT), and it has been shown to be

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effective in the prevention and correction for loss of water and salts in diarrhoeal diseases, including cholera, in adults and children (12-14). G-ORS reduces neither stool volume nor duration of diarrhoea which prompted scientists to identify an alternative ORT which can address the current limitations of ORS. One such alternative has been to replace glucose with rice. In several studies, rice-based ORS (R-ORS) was found to be superior to G-ORS both in cholera due to *V. cholerae* O1 and non-cholera diarrhoea (15,16). Therefore, the primary aim of this study was to evaluate the efficacies of R-ORS and G-ORS in the management of severe cholera due to *V. cholerae* O139 Bengal in adult males.

MATERIALS AND METHODS

Study design and setting

This randomized, controlled clinical trial was conducted at the Clinical Research and Service Centre (CRSC) of ICDDR,B: Centre for Health and Population Research, Dhaka, Bangladesh, during September-November 1995.

Informed written consent was obtained from each patient before enrollment in the study.

Inclusion criteria

Patients were eligible for the study if they were male patients aged 18-60 years, attending CRSC from 9.00 am to 12.00 noon for treatment of watery diarrhoea of less than 16 hours duration, with signs of severe dehydration and presence of *V. cholerae* on dark-field microscopic examination of fresh stool (17,18).

Patients were not eligible for enrollment in the study if they had any concomitant illnesses, including pneumonia, meningitis, clinically-suspected septicaemia, or had received any antimicrobial therapy or ORS for the present illness before reporting to CRSC.

Randomization procedure

A computer-generated randomization plan was used. Patients were assigned a sequential study number, and such numbers were pre-assigned to either R-ORS or G-ORS. A senior staff member, who was not involved in the study in any way, prepared the randomization table and list of subjects' identification numbers with corresponding treatment assignments for individual patients in sealed envelopes that were kept in the pharmacy. The pharmacy provided appropriate ORS corresponding to the identification number of patients enrolled in the study and supplied those to the study nurse when a subject was ready for enrollment in the study. Because of the nature of the suspension formed by rice-ORS, blinding of the treatment regimen was not possible. However, neither the investigators nor the patients and their attendants knew which of the two ORSs a particular patient would receive.

Case management

Upon initial recruitment into the study, patients were weighed on an electronic weighing scale (Sartorius, Gottingen, Germany) with 10 g precision and were placed on a cholera cot (19). A research physician obtained the medical history either from the patients or from their attendants, performed thorough physical examinations, including assessment of dehydration, following the WHO guidelines (20), and recorded all the findings on pre-designed and pre-tested forms. Patients were then rehydrated within 3-4 hours using an intravenous (i.v.) polyelectrolyte solution (sodium 133 mmol/L, potassium 13 mmol/L, chloride 98 mmol/L, and sodium acetate 48 mmol/L) according to the WHO guidelines (21). After initial hydration, patients were reweighed and observed for a further four hours during which their ongoing stool loss was corrected using the same i.v. solution. Patients with a purging rate of ≥5 g/kg.hour during the observation period were enrolled in the study, and the time was designated as '0 hour'. At this point, a stool sample was sent to the laboratory for culture and body weight of the patients was taken again, and the study subjects were randomized to receive one of two therapies: R-ORS [sodium 90 mmol/L, potassium 20 mmol/L, chloride 80 mmol/L, citrate 10 mmol/L, and rice-powder 50 g/L] or WHO-recommended G-ORS [sodium 90 mmol/L, potassium 20 mmol/L, chloride 80 mmol/L, citrate 10 mmol/L, and 20 g of glucose/L] which they were allowed to take according to the WHO treatment plan B (20). Patients were also offered normal hospital diet (rice, bread, curry) and plain water freely along with the assigned ORS and were also given tetracycline capsule 500 mg 6 hourly for 3 consecutive days. Patients who failed to remain hydrated with ORT according to the WHO criteria were again rehydrated with i.v. fluid and switched to ORT again. The study nurses offered the assigned ORS to patients, and the same formulation was continued throughout the study period for that particular patient.

Outcome measures

All stools of patients were collected in a bucket and weighed in a balance with a precision of ±05 g (Sartorius,

Gottingen, Germany) for each 8-hour period starting from '0 hour' and recorded by nurses who were trained for this study. The same nurses similarly recorded stool consistency, fluid intake, and urine output until 72 hours.

'Diarrhoea' was defined as passage of at least one liquid stool per day, irrespective of the volume. 'Formed stool' was defined as one that retains its shape and 'soft stool' one that sticks to and takes the shape of the container; 'liquid stool' as one that can be poured like water from one container to another. Unscheduled i.v. therapy or treatment failure was defined as a condition when re-institution of i.v. fluid therapy was required at any time after the '0 hour' due to the failure of patients to maintain hydration with ORS; this was determined by a physician according to the WHO guidelines (21).

'Duration of diarrhoea' was defined as the interval between '0 hour' and the end of the last 8-hour period when a liquid stool has been passed followed by no liquid stool during the next two consecutive 8-hour periods.

End point

The study subjects whose stool culture revealed *V. cholerae* O139 Bengal following a standard laboratory method (22-24) constituted the final study subjects and were followed up to the end of the study, and the study was declared completed 24 hours after resolution of diarrhoea.

Statistical analysis

The primary outcomes for observation in this study were stool output during the first 24 hours after intervention and incidence of unscheduled i.v. fluid (a proxy for treatment failure) during the first 24 hours after randomization and duration of diarrhoea. A sample size of 57 in each treatment group was estimated to detect a 35% difference in stool output between the R-ORS group and the G-ORS group. This sample size was also sufficient to detect a 30% difference on unscheduled i.v. requirement between the groups. To adjust for non-participation because of exclusion criteria, we increased our sample size by 40% of the estimated sample size. For calculation of sample size, we used the reports of Bhattacharya (9) and Molla (15) for stool output and incidence of unscheduled i.v. fluid respectively. The study was designed to have 80% power at 5% significance level.

Edited data from the case report forms were entered into a personal computer using the STATA software package (STATA Statistical Software: release 5.0, College Station, TX, USA). The differences between the groups for normally-distributed continuous variables were tested using Student's *t*-test, and the Wilcoxon rank-sum test was used for comparing continuous variables that were not normally distributed. Chi-square test was performed to assess the significance of differences in proportions between the two study groups, and Fisher's exact test was performed when the predicted numbers per cell in any group was 5 or less. All tests were two-tailed, and the differences in values were considered significant if p was ≤ 0.05.

RESULTS

The figure shows the number of patients who attended the outpatient department of CRSC from 9:00 am to 12:00 noon during the study period, fulfilled the inclusion criteria, and were randomized to receive R-ORS or G-ORS after four hours of observation. The figure also shows the number of patients analyzed finally, whose stool culture yielded *V. cholerae* O139. Both the groups were comparable with regard to their admission characteristics and purging rates during the 4-hour observation period (Table 1).

No significant difference in the median (inter-quartile range) stool output was observed during the first 24 hours after initiation of intervention [179 (67-206) g/kg.24 hour in R-ORS group vs 193 (80-237) g/kg.24 hour in G-ORS group; p=0.52] (Table 2).

Twenty-one percent (12/57) of the study subjects in the R-ORS group and 25% (14/56) in the G-ORS group were considered to have had treatment failure (Table 2) as they received unscheduled i.v. fluid. All treatment failures occurred within the first 16 hours after randomization, mostly during the first 8 hours (11 in each group).

No significant differences in the median (inter-quartile range) duration of diarrhoea and mean body weight gain at discharge were observed between the groups (Table 2).

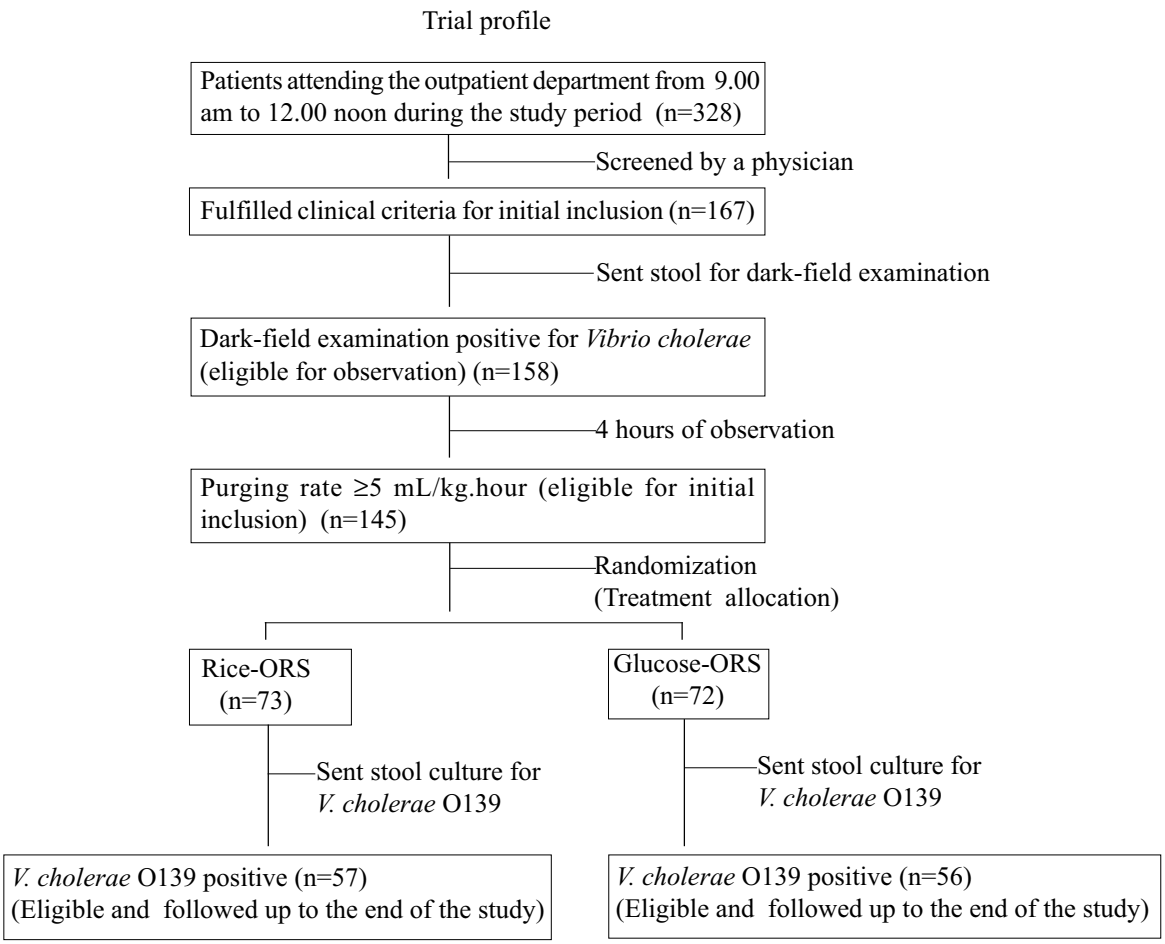
DISCUSSION

V. cholerae O139 Bengal, a bacterial agent that causes outbreaks of cholera, emerged in 1992-1993 in many developing countries. In a diarrhoeal disease hospital in Bangladesh, currently about 5.0% of patients attend with diarrhoea due to *V. cholerae* O139 Bengal (ICDDR,B diarrhoeal disease surveillance report, May 2003).

Cholera patients with mild-to-moderate severity can be successfully treated with WHO-recommended G-ORS. However, R-ORS has been reported to be superior to G-ORS in the management of cholera due to *V. cholerae* O1 (25). Because of the similarities in the pathogenesis and clinical features of diarrhoea due to *V. cholerae* O139 and *V. cholerae* O1, similar therapeutic responses were expected to be observed with regard to R-ORS in both the infections. In this trial, in severe cholera due to *V. cholerae* O139 Bengal, we did not find a significant benefit of R-ORS over G-ORS in reducing stool volume, incidence of unscheduled i.v. fluid, and duration of diarrhoea.

In a systematic review of reports on controlled trials that compared the effects of R-ORS and G-ORS in cholera due to *V. cholera* O1, a 28-44% reduction in stool volume in adults and a 6-36% reduction in children have been reported (25). In non-cholera diarrhoea, use of R-ORS resulted in a 6-30% reduction in stool volume (25). In one study, positive effect of rice-ORS on the reduction of stool volume was observed within 24 hours of administration of R-ORS (25). Another recent study reported a 20% reduction in stool volume during the first 8 hours in children with diarrhoea managed with packaged rice-ORS (26). In our study, we did not observe superior effects of R-ORS over G-ORS in reducing stool volume in adults with severe cholera due to *V. cholerae* O139 Bengal at any given 8 hour-period or during the whole observation period. The reasons for the discrepancies between the findings of earlier studies and our study cannot be delineated from the type of our study design. However, the difference could, at least in part, be due to early resumption of feeding and early

Fig. Patient flow diagram



administration of an effective antimicrobial agent in our study. The diets given in our hospital are mainly rice-based which might have acted like rice-ORS and, thus, to that reported in earlier studies where ORS was used as the maintenance fluid after an initial correction for dehydration in patients with severe cholera and cholera-

Table 1. Baseline characteristics of study subjects

Characteristics	R-ORS group (n=57)	G-ORS group (n=56)
Age (years)	31.70±9.90	34.46±9.43
Body weight (kg)	43.63±5.61	42.91±4.79
Pre-admission duration of diarrhoea (hours)	09.67±5.12	10.25±5.38
Pre-admission no. of stools	10 (8-12)	9 (7-15)
No. (%) of patients with vomiting	55 (97)	52 (93)
No. (%) of patients with nausea	51 (89)	45 (80)
Severe dehydration	57 (100)	56 (100)
Characteristics at the end of 4-hour observation period		
Body weight (kg)	48.84±6.41	47.83±5.34
Body weight gain (% increased from admission weight)	11.90±1.38	11.45±1.32
Volume of stool passed (g/kg.h)	14.82±7.61	13.02±6.45
Volume of intravenous fluid intake (mL/kg.h)	16.96±4.39	15.39±5.0

Values are mean±SD or median (inter-quartile range) or no. (%)
G-ORS=Glucose-based oral rehydration solution
R-ORS=Rice-based oral rehydration solution
SD=Standard deviation

Table 2. Stool output, fluid intake, incidence of unscheduled i.v. fluid, duration of diarrhoea, and body weight at the end of the study

Outcome	R-ORS group (n=57)	G-ORS group (n=56)	p value
Stool output (g/kg.24 h)			
First 24 hours	179 (67-207)	193 (80-237)	0.52
Second 24 hours	20 (10-42)	22 (8-34)	0.62
Third 24 hours	0 (0-0)	0 (0-0)	0.67
Total stool (g/kg.72 h)	210 (82-253)	224 (88-277)	0.65
ORS intake (mL/kg.24 h)			
First 24 hours	191 (86-276)	209 (88-242)	0.56
Second 24 hours	23 (13-45)	22 (9-34)	0.43
Third 24 hours	0 (0-11)	0 (0-17)	0.49
Total (mL/kg.72 h)	228 (108-325)	234 (106-278)	0.86
Unscheduled i.v. fluid during entire study period, no. (%)	12 (21)	14 (25)	0.78
Median (inter-quartile range) duration of diarrhoea (hours)	32 (24-48)	32 (24-56)	0.64
Mean±SD body weight gain on discharge (as % increased from admission body weight)	9.20±3.7	9.98±3.4	0.33

Values are median (inter-quartile range) or mean±SD or no. (%)
G-ORS=Glucose-based oral rehydration solution
ORS=Oral rehydration solution
R=ORS=Rice-based oral rehydration solution
SD=Standard deviation

might have narrowed the differences in stool volumes in our study. Both food and antibiotics have an effect in reducing stool volume (27-29) and, therefore, the effects of these factors might have been responsible for masking the effects of the two types of ORS.

In our study, incidence of unscheduled i.v. fluid was 21% (12/57) in the R-ORS group and 25% (14/56) in the G-ORS group, and the treatment failures were similar

like diarrhoea (15). Vomiting, a common presentation in the early phase of cholera, was also a persistent symptom in our study patients during the first 8 hours, which would likely be an important cause for requirement of unscheduled i.v. therapy in both the groups.

Most previous studies reported a 5-19% (average 12%) reduction in the duration of diarrhoea among patients treated with R-ORS over those treated with G-ORS

(14,25), irrespective of aetiology of diarrhoea and age of patients. Our study failed to observe a significant difference in the median duration of diarrhoea between the two treatment groups. This is likely due to the fact that we studied only patients with culture-proved *V. cholerae* O139 Bengal unlike other studies, and all of our study patients had a high purging rate (>13 g/kg.h). Moreover, early administration of tetracycline in our study might be another possible cause of failure to demonstrate the differences in the duration of diarrhoea between the groups.

In conclusion, the results of our study indicate that rice-ORS is as efficacious as, but not better than, standard glucose-based solution in the management of severe cholera due to *V. cholerae* O139 Bengal in adult males. Therefore, in communities where both *V. cholerae* O139 and *V. cholerae* O1 coexist, a better option for the management of cholera would be an early introduction of an easily available ORT along with an early introduction of food and an effective antibiotic.

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REFERENCES

1. Ramamurthy T, Garg S, Sharma R, Bhattacharya SK, Nair GB, Shimada T *et al.* Emergence of novel strain of *Vibrio cholerae* with epidemic potential in southern and eastern India (letter). *Lancet* 1993;341:703-4.
2. Nair GB, Ramamurthy T, Bhattacharya SK, Mukhopadhyay AK, Garg S, Bhattacharya MK *et al.* Spread of *Vibrio cholerae* O139 Bengal in India. *J Infect Dis* 1994;169:1029-34.
3. Bhattacharya MK, Bhattacharya SK, Garg S, Saha PK, Dutta D, Nair GB *et al.* Outbreak of *Vibrio cholerae* non-O1 in India and Bangladesh. *Lancet* 1993;341:1346-7.
4. Albert MJ, Siddique AK, Islam MS, Faruque AS, Ansaruzzaman M, Faruque SM *et al.* Large outbreak of clinical cholera due to *Vibrio cholerae* non-O1 in Bangladesh. *Lancet* 1993;341:704.
5. Mahalanabis D, Faruque ASG, Albert MJ, Salam MA, Hoque SS. An epidemic of cholera due to *Vibrio cholerae* O139 in Dhaka, Bangladesh: clinical and epidemiological features. *Epidemiol Infect* 1994;112:463-71.
6. Siddique AK, Zaman K, Akram K, Mutsuddy P, Eusof A, Sack RB. Emergence of a new epidemic strain of *Vibrio cholerae* in Bangladesh: an epidemiological study. *Trop Geogr Med* 1994;46:147-50.
7. Higa N, Honma Y, Albert MJ, Iwanaga M. Characterization of *Vibrio cholerae* O139 synonym Bengal isolated from patients with cholera-like disease in Bangladesh. *Microbiol Immunol* 1993;37:971-4.
8. Cholera Working Group (Albert MJ, Ansaruzzaman M, Bardhan PK, Faruque ASG, Faruque SM, Islam MS *et al.*). Large epidemic of cholera-like disease in Bangladesh caused by *Vibrio cholerae* O139 synonym Bengal. *Lancet* 1993;342:387-90.
9. Bhattacharya SK, Bhattacharya MK, Nair GB, Dutta D, Deb A, Ramamurthy T *et al*. Clinical profile of acute diarrhea cases infected with the new epidemic strain of *Vibrio cholerae* O139: designation of the disease as cholera. *J Infect* 1993;27:11-5.
10. Dhar U, Bennish ML, Khan WA, Seas C, Khan EH, Albert MJ *et al.* Clinical features, antimicrobial susceptibility and toxin production in *Vibrio cholerae* O139 infection: comparison with *V. cholerae* O1 infection. *Trans R Soc Trop Med Hyg* 1996;90:402-5.
11. Hossain MS, Salam MA, Rabbani GH, Biswas R, Mahalanabis D. *Vibrio cholerae* O139 Bengal: a descriptive study. *J Health Popul Nutr* 2000;18:27-32.
12. Nalin DR, Cash RA, Islam R, Molla M, Phillips RA. Oral maintenance therapy for cholera in adults. *Lancet* 1968;2:370-3.
13. Chatterjee A, Mahalanabis D, Jalan KN, Maitra TK, Agarwal SK, Bagchi DK *et al.* Evaluation of a sucrose/electrolyte solution for oral rehydration in acute infantile diarrhoea. *Lancet* 1977;1:1333-5.
14. Fontaine O, Gore SM, Pierce NF. Rice-based oral rehydration solution for treating diarrhea. *Cochrane Database Syst Rev* 2000;(2):CD001264.
15. Molla AM, Sarker SA, Hossain M, Molla A, Greenough WB, III. Rice-powder electrolyte solution as oral therapy in diarrhoea due to *Vibrio cholerae* and *Escherichia coli*. *Lancet* 1982;1:1317-9.

16. Molla AM, Ahmed SM, Greenough WB, III. Rice-based oral rehydration solution decreases the stool volume in acute diarrhea. *Bull World Health Organ* 1985;63:751-6.
17. McArthur J. The rapid diagnosis of cholera. *J Trop Med Hyg* 1977;80:99-101.
18. Benenson AS, Islam MR, Greenough WB, III. Rapid identification of *V. cholerae* by dark field microscopy. *Bull World Health Organ* 1964;30:721-9.
19. Greenough WB, III. *Vibrio cholerae*. Dhaka: International Centre for Diarrhoeal Disease Research, Bangladesh, 1979. 38 p. (ICDDR,B scientific report no. 22).
20. World Health Organization. A manual for the treatment of acute diarrhea. Geneva: Programme for the Control of Diarrhoeal diseases, World Health Organization, 1984. 25 p. (WHO/CDD/SER/80.2 REV.I).
21. World Health Organizaton. Programme for the Control of Diarrhoeal Diseases. A manual for the treatment of diarrhea: for use by physicians and other health workers. Geneva: World Health Organization, 1990. 46 p. (WHO/CDD/SER/80-2. Rev.2, 1990).
22. World Health Organization. Programme for the Control of Diarrhoeal Diseases. Manual for laboratory investigations of acute enteric infections. Geneva: World Health Organization, 1987. 111 p. (CDD)/83.3 Rev.1).
23. Qadri F, Hasan JAK, Hossain J, Chowdhury A, Begum YA, Azim T *et al*. Evaluation of the monoclonal antibody-based kit Bengal SMART for rapid detection of *Vibrio cholerae* O139 synonym Bengal in stool samples. *J Clin Microbiol* 1995;33:732-4.
24. Qadri F, Chowdhury A, Hossain J, Chowdhury K, Azim T, Shimada T *et al*. Development and evaluation of rapid monoclonal antibody-based coagglutination test for direct detection of *Vibrio cholerae* O139 synonym Bengal in stool samples. *J Clin Microbiol* 1994;32:1589-90.
25. Gore SM, Fontaine O, Pierce NF. Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. *Br Med J* 1992;304:287-91.
26. Zaman K, Yunus M, Rahman A, Chowdhury HR, Sack DA. Efficacy of a packaged rice oral rehydration solution among children with cholera and cholera-like illness. *Acta Paediatr* 2001;90:505-10.
27. Fayad IM, Hashem M, Duggan C, Refat M, Bakir M, Fontaine O *et al.* Comparative efficacy of rice-based and glucose-based oral rehydration salts plus early reintroduction of food. *Lancet* 1993;342:772-5.
28. Santosham M, Fayad IM, Hashem M, Goepp JG, Refat M, Sack RB. A comparison of rice-based oral rehydration solution and "early feeding" for the treatment of acute diarrhea in infants. *J Pediatr* 1990;116:868-75.
29. Hossain MS, Salam MA, Rabbani GH, Kabir I, Biswas R, Mahalanabis D. Tetracycline in the treatment of severe cholera due to *Vibrio cholerae* O139 Bengal. *J Health Popul Nutr* 2002;20:18-25.