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Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials

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Abstract

Objective—To define the benefit of rice oral rehydration salts solution in relation to the glucose based World Health Organisation oral rehydration salts solution for treating and preventing dehydration in patients with severe dehydrating diarrhoea.

Design—Meta-analysis using data from 13 available randomised trials that compared these two formulations.

Subjects—The studies compared 1367 patients with cholera, severe cholera-like diarrhoea, or acute non-cholera diarrhoea. 668 received the standard WHO solution and 699 the rice based solution.

Intervention—Each trial report was reviewed to determine patient eligibility, the number of patients who were randomised and the number of these excluded from analysis, details of the randomisation procedure, and the precise timing of the outcome measurements.

Main outcome measures—Stool output during the first 24 hours; weighted estimates of the difference in mean stool output between treatments.

Results—The rice solution significantly reduced the rate of stool output during the first 24 hours by 36% (95% confidence interval 28 to 44%) in adults with cholera and by 32% (19 to 45%) in children with cholera. The rate of stool loss in infants and children with acute non-cholera diarrhoea was reduced by only 18% (6 to 30%).

Conclusions—The benefit of rice oral rehydration salts solution for patients with cholera is sufficiently great to warrant its use in such patients. The benefit is considerably smaller for children with acute, non-cholera diarrhoea and should be more precisely defined before its practical value can be judged.

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Introduction

Oral rehydration therapy with the glucose and electrolyte solution recommended by the World Health Organisation and Unicef is the preferred method for treating children with dehydration due to diarrhoea, provided that they are able to drink and do not have signs of shock.[1] Although the solution is both safe and effective (D Mahalanabis, unpublished WHO document), it has important limitations: it neither reduces the rate of stool loss nor shortens the duration of illness.[2-5] Mothers often do not understand the relation between diarrhoea and dehydration, and their primary concern, shared by many health workers, is to see the diarrhoea stop. This probably accounts for the continuing widespread use of ineffective "antidiarrhoeal" drugs and antibiotics to treat diarrhoea instead of, or in addition to, oral rehydration salts solution (WHO diarrhoeal diseases control programme, seventh programme report, 1988-89, 1990).

If a packaged oral rehydration salts formulation could be developed that not only had the positive features of the WHO formulation, including low cost and safety and stability during prolonged storage, but also substantially reduced the duration of diarrhoea or the rate of stool loss, it would have considerable advantages. In particular, it could be promoted as having a real antidiarrhoeal effect. This should improve its acceptance and use by both health workers and mothers, especially if its benefits were sufficiently great to be evident to them. It might also result in less use of ineffective drugs and antibiotics. Such changes would represent a major advance in efforts to control morbidity and mortality associated with diarrhoea through effective case management.

Several clinical trials have shown that an oral rehydration salts solution containing cooked rice powder (50-80 g/l) in place of the usual glucose (20 g/l) substantially reduces the rate of stool loss due to acute diarrhoea.[6-10] Other studies, however, have reported no significant benefit.[11-14] The subjects in these studies varied considerably and included infants, children, and adults both with diarrhoea associated with cholera and with acute diarrhoea not associated with cholera. Moreover, in some studies the number of patients evaluated was probably insufficient to support firm conclusions. To define more precisely the true benefit of rice oral rehydration salts solution in relation to the WHO oral rehydration salts solution and to determine whether this benefit is related to the patient's age or the aetiology of diarrhoea we performed a meta-analysis by using data from all available randomised clinical trials that compared these two formulations.

Methods

SELECTION OF TRIALS

Studies included in this overview were identified by a computer aided search of the published work, by reviewing the references cited in relevant reports, and by inquiring about completed but unpublished studies from our colleagues. Ten published reports[6-15] and three unpublished ones (A M Moechtar, E Guiraldes, and N H Alam, personal communications) were identified and are reviewed in this analysis. On the basis of their design or method of analysis these 13 studies yielded 17 comparisons between patient groups treated with rice oral rehydration salts or the WHO oral rehydration salts solution. Table I gives the principal features of each comparison. In all cases the studies were randomised trials that compared standard WHO oral rehydration salts solution with an experimental oral rehydration salts solution in which glucose (20 g/l) was replaced by 50-80 g/l of rice powder, the electrolyte concentrations remaining unchanged. In early studies (A N Alam, personal communication)[8-11 13-15] the rice powder was cooked immediately before use and salts were added after the rice solution had cooled. In the most recent[6 12] (Moechtar *et al*, Guiraldes *et al*) a commercially produced, precooked rice powder was prepackaged with oral rehydration salts, in sachets to make up one litre. This was prepared for use in the same way as standard WHO oral rehydration salts, as precooked rice dissolves rapidly in cold water.

TABLE I—*Characteristics of randomised trials of rice oral rehydration solution*

Comparison	Age	Dehydration	Cholera (proportion proved on culture)	Amount of rice in solution (g/l)	No randomised to WHO/rice solution (No excluded)
			Patients with cholera or cholera-like illness		
Moechtar *et al* (1)*	>12 years	Severe	Yes	50	83/81 (0/0)
Moechtar *et al* (2)*	>12 years	Severe	No	50	12/14 (0/0)
Alam *et al* (1)†	Adults	Moderate to severe	Yes	50	47/46 (?)
Alam *et al* (2)†	Adults	Moderate to severe	Yes	50	42/47 (?)
Molla *et al* (1)[8]*	>10 years	Moderate to severe	Yes (65%)	80	74/85 (2/0)
Molla *et al* (2)[8]*	?-<10 years	Moderate to severe	Yes (75%)	80	105/84 (4/0)
Molla *et al* (3)[10]	1-5 years	Moderate to severe	Yes (55%)	50	42/37 (?)
Molla (4)[7]	2-5 years	Moderate to severe	Yes (80%)	80	25/27 (0/0)
Alam (3)[9]*	1-8 years	Moderate to severe	Yes (100%)	50	19/20 (2/2)
Alam (4)[9]*	1-8 years	Moderate to severe	No	50	7/6 (0/0)
Patra *et al*[6]	3 months-5 years	Moderate to severe	Yes (30%)	50	26/26 (2/2)
			Patients without cholera		
Guiraldes *et al*	4-24 months	Moderate	No	50	49/51 (1/2)
Kenya *et al*[14]	4-59 months	Moderate to severe	No	60	50/51 (1/1)
Dutta *et al*[12]	4 months-4 years	Moderate	No	50	33/37 (0/0)
Bhan *et al*[11]	3 months-5 years	Moderate	No	50	33/31 (0/0)
El Mougi *et al*[15]	4-18 months	Moderate	No	50	30/30 (4/5)
Mohan *et al*[13]	3 months-3 years	Mild to severe	No	50	24/26 (1/3)

*Single studies in which results were stratified for analysis.
†Clinical trial with a factorial design (4 cell trial).

To our knowledge no other randomised trials of these formulations of rice oral rehydration salts solution have been completed, although several are underway. We have not included three trials of solutions that contained only 30 g/l of rice powder (O Fontaine, personal communication)[12 16] and one of an oral rehydration salts solution containing rice powder and glycine.[17]

Each trial report was reviewed independently by a statistician (SMG) and a clinician (OF) to determine patient eligibility according to stated selection criteria for age and dehydration status; the number of patients who were randomised and the number of these subsequently excluded from analysis; details of the randomisation procedure; and the precise timing of the outcome measurements, such as stool output and intake of oral rehydration salts solution.

META-ANALYSIS

Each of the 17 comparisons yielded an estimate of the true difference in mean stool output between patients treated with the two different salts solutions; and each difference in means (D_i for comparison i) is qualified by a variance:

$$\text{var}(D_i)=(se_i)^2$$

The larger the variance, the less precise is the observed difference as an estimate of the true difference in mean stool output between treatment groups. It follows that the amount of information conveyed by a single comparison about this true difference is inversely proportional to the variance of the estimated difference for that comparison. If the inverse of the variance is taken as a measure of the information contained in comparison i, then the weight (w_i) that should be accorded to comparison i, among all comparisons in its set, may be taken to be the information in comparison i divided by the total information (that is, the sum over all comparisons i=1, 2, . . . n of the inverse of the variances):

$$w_i=[(1/se_i)^2]/\Sigma_{i=1}^{n}(1/se_i)^2$$

Clearly, these weights add up to one. A pooled or weighted estimate of the difference in mean stool output between patients treated with rice oral rehydration salts solution or WHO oral rehydration salts solution is obtained by summing the differences in individual comparisons, each multiplied by its corresponding weight, so that if a single comparison accounts for 10% of the information then 10% of its estimated difference counts towards the pooled estimate. With the foregoing choice of weights, the variance of the pooled difference has a particularly simple form. Just as we defined information as the inverse of variance, so the variance of the pooled estimate is the inverse of the total information:

$$\text{var (pooled difference)}= \text{var}\ \Sigma_{i=1}^{n} w_i D_i=1/\Sigma_{i=1}^{n}(1/se_i)^2$$

A 95% confidence interval for the pooled estimate runs from two standard errors below the pooled estimate to two standard errors above, where the standard error is the square root of the variance of the pooled estimate.

Results

EVALUATION OF TRIALS

The review identified problems in both the design and the analysis of some trials. These are summarised below.

Randomisation

The randomisation of patients should have occurred

TABLE II—*Stool output in first 24 hours in adults with diarrhoea associated with cholera or cholera-like illness*

Comparison	No analysed taking WHO/rice solution	Treatment with WHO solution: Mean (SD) stool output (g or ml/kg in first 24 h)	Mean stool output/SD	Mean stool output/ mean intake of solution	Mean reduction (variance) in stool output during treatment with rice solution (g or ml/kg)	Study weight
Moechtar *et al* (1) 6-24 hours	83/81	133 (92)	1·4	0·63	39 (148)	0·45
Moechtar *et al* (2) 6-24 hours	12/14	106 (55)	1·9	0·63	48 (407)	0·16
Alam *et al* (1)	47/46	391 (157)	2·5	0·75	164 (829)	0·08
Alam *et al* (2)	42/47	366 (174)	2·1	0·81	144 (1068)	0·06
Molla *et al* (1)[8]	72/85	159 (109)	1·5	0·64	44 (266)	0·25

TABLE III—*Stool output in first 24 hours in children with diarrhoea associated with cholera or cholera-like illness*

Comparison	No analysed taking WHO/rice solution	Treatment with WHO solution: Mean (SD) stool output (g or ml/kg in first 24 h)	Mean stool output/SD	Mean stool output/ mean intake of solution	Mean reduction (variance) in stool output during treatment with rice solution (g or ml/kg)	Study weight
Molla *et al* (2)[8]	101/84	204 (140)	1·5	0·54	49 (362)	0·42
Molla *et al* (3)[10]	42/37	343 (151)	2·3	1·49	181 (628)	Zero
Molla *et al* (4)[7]	25/27	210 (158)	1·3	0·69	105 (1206)	0·12
Alam *et al* (3)[6]*	19/20	290 (190)	1·5	0·98	160 (2500)	0·06
Alam *et al* (4)[6]*	7/6	90 (75)	1·2	0·57	−40 (700)	0·21
Patra *et al*[6]	24/24	166 (114)	1·5	0·62	69 (794)	0·19

*Data not reported quantitatively; values in this table are approximated from graphic presentation.

TABLE IV—*Stool output in first 24 hours in children with diarrhoea not associated with cholera*

Comparison	No analysed taking WHO/rice solution	Treatment with WHO solution: Mean (SD) stool output (g or ml/kg in first 24 h)	Mean stool output/SD	Mean stool output/ mean intake of solution	Mean reduction (variance) in stool output during treatment with rice solution (g or ml/kg)	Study weight
Guiraldes *et al*	48/49	126 (64)	2·0	0·30	14 (219)	0·21
Kenya *et al*[14]	49/50	103 (31)	3·3	0·48	3 (35)	Zero
Dutta *et al*[12]	33/37	103 (55)	1·9	0·60	17 (145)	0·32
Bhan *et al*[11]	33/31	77 (58)	1·3	0·49	10 (161)	0·29
El Mougi *et al*[15]	26/25	245 (129)*	1·9	0·72	82 (1115)	0·04
Mohan *et al*[13]	23/23	110 (69)	1·6		22 (340)	0·14

*The reported SD (25·3) was very low in relation to the large observed difference in stool output; we assumed that the reported SD values were actually SEs and revised the SDs accordingly.

immediately before treatment with oral rehydration salts solution began—that is, after the completion of any intravenous treatment for severe dehydration. However, in no trial was it stated when patients with severe dehydration were randomised and outcome measurements initiated—that is, before or after initial intravenous rehydration. Thus it was unclear whether the first 24 hour measurement of stool output began when intravenous rehydration was started or when oral rehydration salts solution was first given, as should have been the case.

In one study patients were randomised irrespective of age, but were stratified into arbitrary age groups during analysis.[8] Ideally, such stratification should have been part of the randomisation plan. Stratification during analysis was also done in two other studies (Moechtar *et al*),[9] but this was based on aetiology and so was unavoidable.

Exclusion from analysis

Pragmatic analysis according to intention to treat requires that all randomised patients continue to be monitored and that their data be included in the analysis. Nevertheless, in seven trials (Guiraldes *et al*)[6 8 9 13-15] 1-15% of randomised patients were excluded from the analysis (table I), either because they were considered to be "treatment failures" (usually because additional intravenous treatment was required) or because they had been randomised in error. In two trials that used a permuted block[10] or factorial design (Alam *et al*) it seems that some patients were randomised but not reported on, as the numbers specified in the different treatment groups differed appreciably. The reasons for these differences were not stated.

Analysis and internal consistency of outcome data

Whereas all studies reported stool output and oral rehydration salts solution intake during the first 24 hours, few reported total stool output until diarrhoea stopped, and only seven studies reported the duration of diarrhoea. Our analysis therefore focused largely on stool output during the first 24 hours. The following results for the first 24 hours are reported: mean (standard deviation) stool output (in g or ml/kg body weight) for patients randomised to WHO oral rehydration salts solution; the ratio of mean stool output to its standard deviation; the ratio of mean stool output to mean intake of WHO oral rehydration salts solution; and the mean reduction in stool output (in g or ml/kg) for patients given rice oral rehydration salts solution compared with those given WHO oral rehydration salts solution, and the variance of that value.

Tables II, III, and IV show the mean (SD) stool output (in g or ml/kg) during the first 24 hours for patients in each study who were randomised to receive WHO oral rehydration salts solution. Whether the data were for adults with cholera or with cholera-like diarrhoea (severe dehydrating diarrhoea, clinically resembling that associated with cholera but from which *Vibrio cholerae* 01 was not isolated) (table II), children with cholera or cholera-like diarrhoea (table III), or children with only acute non-cholera diarrhoea (table IV), the ratios of mean to standard deviation for stool output were roughly constant, averaging 1·6 and ranging (with one exception) from 1·2 to 2·5. This regularity indicates the need for logarithmic transformation; however, no study reported logarithmically transformed data or performed calculations on that scale. This finding also provides a criterion for judging the internal consistency of key outcome data. By this criterion one trial seems to be atypical with a ratio of 3·3,[14] twice the mean value reported in other studies. Even more extreme was the ratio of 10 from the data reported in another study.[15] We suspected confusion between standard error and standard deviation in this study, and therefore table IV shows what we believe to be the correct standard deviation for this trial, a value similar to those in the other studies.

Tables II, III, and IV also show a second measure by which to assess the internal consistency of trial data—namely, the ratio of mean stool output to mean intake of WHO oral rehydration solution. Mean stool output averages about two thirds of mean oral rehydration salts solution intake. By this criterion one trial seems to be atypical,[10] the mean stool output being almost 50% greater than the mean intake of oral rehydration salts solution (table III). In the analyses that follow, two studies[10 14] have been excluded (that is, zero weighted) for the reasons mentioned above.

SUBSTANTIVE RESULTS

The results of the analysis of stool output and intake of oral rehydration salts solutions during the first 24 hours have been grouped into three sets according to the patient's age and aetiology of diarrhoea, as shown in tables II, III, and IV. For the duration of diarrhoea all data have been combined, but comparisons in patients with suspected cholera who received tetracycline before diarrhoea stopped have been zero weighted (table V).

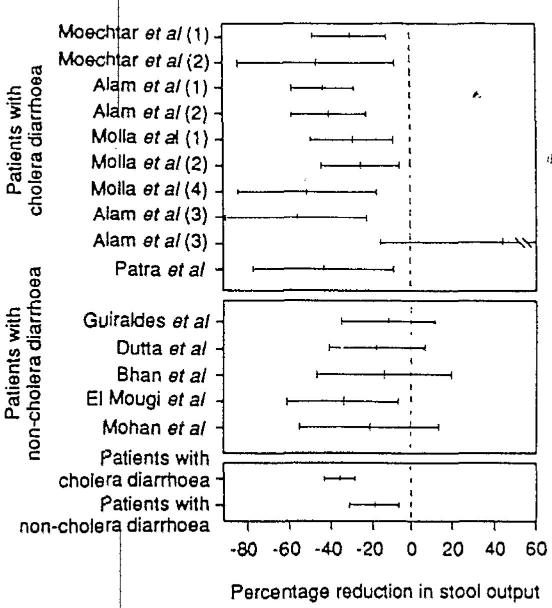
Adults with cholera or cholera-like diarrhoea—Table II shows the weights assigned to each of the five comparisons in this set. By using these weights the estimated mean stool output for patients given WHO oral rehydration salts solution was 170 ml/kg. For patients given rice oral rehydration salts solution this was reduced by a mean of 58 ml/kg (36%, 95% confidence interval 28 to 44%).

Children with cholera or cholera-like diarrhoea—Table III shows the weights assigned to each of the five comparisons in this set. One study[15] was zero weighted for reasons described above. With those weights the estimated mean stool output for patients given the WHO oral solution was 178 ml/kg. For patients given the rice solution this was reduced by a mean of 48 ml/kg (32%, 19% to 45%).

Children with non-cholera diarrhoea—In this set of six comparisons, one study[14] was zero weighted for reasons described above (table IV). By using the weights calculated for the other five comparisons the estimated mean stool output for patients given the WHO solution was 107 ml/kg. For patients given the rice solution this was reduced by a mean of 18 ml/kg (18%; 6% to 30%). It is noteworthy that the estimated mean percentage reduction in stool output associated with the rice solution in the zero weighted study is outside the 95% confidence interval derived from the other five studies.

Overall reduction in stool output—The figure presents the percentage reduction in mean stool output (with 95% confidence intervals) for patients treated with the rice solution in each of the comparisons considered in this overview, as well as the pooled (weighted) estimates of the percentage reduction in mean stool output for patients with cholera (adults and children) and without cholera (details of these calculations are not shown). The effect of the rice solution on stool output was significantly less in children with non-cholera diarrhoea than in children and adults with cholera or cholera-like diarrhoea (95% confidence interval 3% to 31% for the difference in percentage reduction in stool output in patients with cholera or cholera-like diarrhoea *v* patients with non-cholera diarrhoea).

Duration of diarrhoea—Data from six comparisons, including both adults and children with cholera (who had not received tetracycline before diarrhoea stopped) and acute non-cholera diarrhoea were considered for this analysis (table V). The estimated mean duration in patients given the WHO oral rehydration solution was 68 hours. For those given the rice solution the duration was reduced by a mean of eight hours (12%; 5% to 19%). The 95% confidence interval excludes zero, indicating a modest but significant reduction in the duration of diarrhoea.



Mean percentage reduction in 24 hour stool output in individual studies of adults and children with cholera or cholera-like diarrhoea and children with non-cholera diarrhoea given rice oral rehydration salts solution. Pooled (weighted) estimates of percentage reduction in mean stool output (95% confidence interval) for each group of studies are shown in shaded box

TABLE V—*Duration of diarrhoea*

Comparison	No analysed taking WHO/rice solution	Treatment with WHO solution: Mean (SD) No of patients	Treatment with WHO solution: Mean duration/SD	Mean reduction (variance) duration of diarrhoea with rice solution	Study weight
		Adults with cholera			
Moechtar *et al* (1)	83/81	39 (11)	3·5	2 (3)	Zero
Moechtar *et al* (2)	12/14	36 (7)	5·1	7 (13)	Zero
Alam *et al* (1)	47/46	86 (22)	3·9	9 (26)	0·23
Alam *et al* (2)	42/47	85 (20)	4·2	4 (22)	0·27
		Children with cholera			
Alam *et al* (3)[9]	24/24	90 (43)	2·1	12 (109)	0·05
Patra *et al*[8]	24/24	43 (22)	2·0	13 (36)	0·17
		Children without cholera			
Kenya *et al*[14]	49/50	46 (9)	5·1	4 (4)	Zero
Dutta *et al*[11]	33/37	79 (37)	2·1	10 (67)	0·09
El Mougi *et al*[16]	26/25	34 (12)	2·8	6 (31)	0·19

Discussion

Irrespective of their age, patients with cholera who were given rice oral rehydration salts solution had substantiall lower rates of stool loss than those who were given WHO oral rehydration salts solution. Stool volume was reduced by a mean of 48-58 ml/kg during the first 24 hours of treatment, which was 32-36% less output than for patients given the WHO solution. This presumably reflects the fact that a greater amount of glucose (and amino acids) is released when rice powder is fully digested than is present in the WHO solution. Assuming that glucose facilitated absorption of sodium proceeds on an equimolar basis, 50-80 g/l of rice powder would release sufficient glucose and amino acids to promote the absorption of all the sodium (and water) in the rehydration solution and, in addition, reabsorption of at least part of the sodium (and water) secreted into the bowel as part of the diarrhoeal process, thus diminishing stool output.[18] In contrast, the WHO solution contains only enough glucose (20 g/l) to promote the absorption of the sodium and water in the solution, thus leaving the rate of stool loss essentially unaffected.[19] The lower osmolarity of the rice solution (about 200 mmol/l *v* about 310 mmol/l) would also enhance the intestinal absorption of water, but not of sodium.[20]

In contrast with stool output in cholera patients, that in children with acute non-cholera diarrhoea was reduced by a mean of only 18 ml/kg during the first 24 hours of treatment with rice solution—that is, by 18% compared with that in patients given the WHO solution. The significantly smaller benefit of the rice solution for these patients apparently reflects a partial failure of the process described above. The likely explanations are that, at least in some patients, rice starch and protein were not fully digested, thus reducing the amount of glucose and amino acids available to promote sodium absorption; or released glucose was not fully absorbed; or both. Failure to digest rice powder fully could reflect reduced amylase or disaccharidase activities related to young age, malnutrition, or mucosal damage by the infective agent.[21-23] Mucosal damage could also cause glucose malabsorption, which could exacerbate the rate of stool loss owing to the osmotic activity of unabsorbed glucose in the bowel lumen. If this occurred the adverse effect would be greater for rice oral rehydration salts solution owing to the greater amount of glucose released when rice starch is fully hydrolysed. This meta-analysis affords no insight into which of these mechanisms explains the reduced effect of rice oral rehydration salts on stool loss in patients with acute non-cholera diarrhoea.

The meta-analysis shows that treatment with rice solution reduces both the rate of stool loss and, to a lesser extent, the duration of diarrhoea, as compared with treatment with the WHO solution. Both of these variables independently affect the total output of diarrhoeal stool during the illness. Thus when both are reduced the percentage reduction in total stool output would be greater than the percentage reduction in either of the contributing measurements. This suggests that total output of diarrhoeal stool would be the most important clinical outcome measure when different oral rehydration salts formulations are compared. Unfortunately, this value was reported for only one study reviewed here[6] and for another that compared a sorghum based oral rehydration salts solution with the WHO solution.[24] In both studies the percentage reduction was greater in total stool output than in either the rate of stool loss or duration of diarrhoea.

The last point bears directly on whether the rice solution (or any other cereal based oral rehydration salts solution) would have sufficient advantage over the WHO solution to replace it in routine use at health facilities, especially for treating children with acute non-cholera diarrhoea, who represent the overwhelming majority of cases. The average 18% reduction in initial rate of stool loss, if applied to total stool output, is unlikely to justify the major effort and expense required to change over from glucose to precooked rice in the oral rehydration salts formulation, especially in developing countries. A crude estimation showed that the current cost of commercially prepared oral rehydration salts based on precooked rice would be for each one litre packet about three times the cost of the standard packet of WHO oral rehydration salt packet. On the other hand, if the effect on total stool output is appreciably greater, owing to a concurrent shortening of illness, a change in oral rehydration salts formulation might be justified. This requires further study. In the meantime the current data show that rice oral rehydration salts solution has enough advantage over the WHO oral rehydration salts solution to justify its use in patients with cholera, where this is convenient.

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