Correspondence

Oral Therapy for Cholera: Amino Acids Added to Electrolyte Solutions Containing Rice or Glucose

To the Editor—The study by Rabbani et al. [1] demonstrating that L-histidine–supplemented rice-based oral rehydration solution (ORS) reduces diarrheal volume and duration in patients with cholera is interesting and potentially important, but the article omitted reference to the original demonstration of such an effect when an ORS of glucose and electrolytes with added glycine is used [2–4]. Similar data have been obtained in studies conducted on a more limited scale of added alanine and other potential substrates that are capable of enhancing salt and water absorption during cholera. We agree with Rabbani et al. that glycine, alanine, and possibly other sodium-transport promoters need to be studied further. Additionally, comparative efficacy, safety, and cost/availability studies in patients with cholera (and in patients with diarrhea caused by enterotoxigenic *Escherichia coli*) of glucose- or rice-based ORSs with or without glycine or L-histidine—and possibly other combinations—not only are needed but are long overdue.

We chose glycine as the actively transported amino acid to add to the glucose-electrolyte–based ORS because it is cheap, widely available as a food additive, and, importantly, has the highest amino acid absorption rate in animal models (see figure 53 in Wilson [5]). In our clinical trials [2, 3], the glucose plus glycine ORS resulted in reductions in the volume and duration of cholera diarrhea of 39% and 23%, respectively. In patients with cholera caused by nonvibrio pathogens (later linked chiefly to enterotoxigenic *E. coli*), the respective reductions were 73% and 24%. The reductions in patients with cholera were larger than those reported for L-histidine, a finding that is consistent with animal data on absorption rates [5]; a comparative trial would be needed to confirm this. L-histidine also is an actively transported amino acid, but Rabbani et al. suggested that possible alternative mechanisms of action might be at work. If so, combinations of glucose with glycine plus L-histidine might merit testing. It should be noted that the glucose plus glycine ORS we used in 1970 [2, 3] significantly improved outcomes despite having the highest osmolality of any ORS yet tested (400 and 510 mOsm/kg), illustrating that substrate absorbability trumps osmolality in patients with cholera and nonvibrio cholera.

The refocusing of scientific effort on the identification of the most effective, safe, and practical ORS (a super ORS), coupled with recognition that patients with cholera need an ORS formulation that not only rehydrates but also reduces the volume and duration of diarrhea [6], is useful.

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Reply to Nalin and Cash

To the Editor—We thank Nalin and Cash for their encouraging comments regarding our observations on L-histidine's antidiarrheal effects in patients with cholera [1]. They also commented that some original observations on the effects of glycine-containing oral rehydration solutions (ORSs) reported by them in 1970 [2, 3] were omitted.

In our Discussion section, we summarized their observations from 1970 regarding the antidiarrheal effects of glucose plus glycine ORSs in relation to later studies of the topic that we did cite. The fundamental issue raised by Nalin and Cash is that ORSs containing other amino acids (glycine and alanine) substantially reduced the volume and duration of cholera diarrhea in earlier studies and that these findings need to be confirmed in further studies. We fully agree with this, as we stated in our article.

We also endorse and support the idea of developing the most effective and safe ORS formulation—a super ORS—by specifically examining the effects of different types of sodium-transport promoters (glucose, polymerized glucose, cereals, glycine, alanine, histidine, other peptides, and amino acids) in different settings of intestinal osmolality, infection, and age of the individual. There are many ways to improve ORSs following the basic phys-

iological principle of insuring that an ORS has the maximum ability to absorb sodium without exceeding the optimum luminal osmolality. Mixing of ingredients (polypeptides and polysaccharides) needs to be carefully monitored so that it does not compromise sodium absorption by exceeding the optimum level of osmolality. We agree with and support Nalin and Cash's comment that there is a need for future studies combining L-histidine with other amino acids, such as glycine and alanine, to develop the optimal ORS.

With regard to the mechanism(s) of action of L-histidine, in addition to those we have reported (anti-inflammatory, antioxidant, and anti-cAMP effects), we cannot rule out the possibility that it promotes sodium transport. Similarly, for the reported antisecretory effects of other amino acids, there may be mechanisms other than or in addition to sodium transport that need to be studied.

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