Current Gastroenterology Reports (2019) 21: 67
https://doi.org/10.1007/s11894-019-0734-1

SMALL INTESTINE (D SACHAR, SECTION EDITOR)

Principles and Practice of Oral Rehydration

Sylvia Y. Ofei[1,2] · George J. Fuchs III[1,2]

Published online: 7 December 2019

Abstract

Purpose of Review An understanding of fluid and electrolyte losses from diarrhea and mechanisms of solute cotransport led to development of oral rehydration solution (ORS), representing a watershed in efforts to reduce diarrheal disease morbidity and mortality. This report reviews the scientific rationale and modifications of ORS and barriers to universal application.

Recent Findings Solutions with osmolality and electrolyte composition different from original ORS for routine and unique pathophysiology such as in malnutrition have met with varying success. Following the conceptual rationale of sodium-glucose cotransportation to facilitate water absorption, other cotransporters and formulations have been explored with the aim to improve ORS efficacy and acceptance.

Summary ORS remains the anchor of acute watery diarrhea and dehydration management worldwide. Despite development of different formulations, the current standard solution is the mainstay of treatment for nearly all situations. Efforts to improve oral hydration solution and to increase acceptance and usage are ongoing.

Keywords Oral rehydration solution · Oral rehydration therapy · Dehydration · Watery diarrhea

Introduction

Body water homeostasis involves the control of both intake and absorption governed by the gastrointestinal tract and excretion controlled by the kidney. Maintenance of body water and electrolytes is the result of tightly regulated balances of intakes and outputs mediated by elaborate physiologic mechanisms. Sodium retention causes volume expansion and depletion causes volume contraction. A net negative sodium balance results in a clinical state of extracellular fluid volume contraction, the most common cause worldwide being infectious diarrheal disease and that results in dehydration. Under normal conditions, losses via the gastrointestinal tract are small but can greatly increase in pathologic states such as diarrheal disease. Diarrheal illness is estimated to account for more than a half million deaths per year in children under age 5 years, with the great majority of deaths occurring in developing countries and most of these from dehydration. Even so, childhood mortality due to diarrheal disease has decreased from 4.6 million annually in 1980, while the world's population has increased by about 3.1 billion during the same period. Notably, 54 million fewer of these deaths have been attributed to oral rehydration solution (ORS) [1••].

To more fully appreciate the impact and contributions of oral rehydration therapy (ORT), it is useful to understand the clinical and historical context. During the cholera pandemic of 1829 in Russia and Western Europe, Irish physician William Brooke O'Shaughnessy described the stool water and salt losses and prescribed the use of intravenous (IV) fluid therapy with a resultant decrease in mortality from 70 to 40% [2–4]. While 1968 is often referenced as the date of discovery of oral rehydration therapy (ORT), forms of oral rehydration solutions (ORS) were introduced in the 1940s when Dr. Daniel Darrow advocated for rehydration solutions composed of sodium, potassium, and glucose [4, 5]. Through balance studies, he quantified stool electrolyte losses with diarrheal diseases and implemented corporal replacement of these losses [4]. Glucose was added later, most likely for its nutritional value and prior to the recognition of its property to facilitate sodium

This article is part of the Topical Collection on *Small Intestine*

✉ George J. Fuchs, III
george.fuchs@uky.edu

[1] Department of Pediatrics, University of Kentucky College of Medicine/Kentucky Children's Hospital, Lexington, USA

[2] Pediatric Gastroenterology, Hepatology, and Nutrition, University of Kentucky College of Medicine, 138 Leader Ave, Lexington, KY 40506-9983, USA

and hence water transport. Seminal observations including by Sachar et al. in patients with cholera In the late 1960's, seminal observations by Sachar et al. in patients with cholera provided the scientific rationale for ORS. Sachar et al demonstration that the active intestinal sodium-glucose co-transporter (SGLT-1) is preserved in most diarrheal disease and continues to stimulate resorption of salt and water despite the enormous stool losses of water and electrolytes associated with secretory diarrhea [6–8] (Fig. 1 [9•]). In fasted states or between meals, most NaCl is transported from the lumen via exchange (Na+/H– and Cl–/HCO3–). While sodium transport drives fluid absorption, Cl– excretion is the driving force for fluid secretion. Cl is taken up along the basolateral membrane of the epithelial cell by the electroneutral Na+/K+/2Cl– cotransporter and accumulates within the cell above its electrochemical equilibrium (Fig. 2 [9•]). Once within the cell, Cl exits into the intestinal lumen via Cl channels that open in response to regulatory agonists. Stimulation of active chloride secretion is the underlying pathophysiological mechanism of diarrhea due to *Vibrio cholera* and certain other enteric pathogens. Cholera toxin, Enterotoxigenic Escherichia coli (ETEC) heat-labile enterotoxin (LT), and ETEC heat-stable enterotoxin (ST) invoke second messenger systems and excessive activation of cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels while rotavirus diarrhea is mediated by calcium-activated chloride channels. Cholera toxin and ETEC LT are similar physiologically, structurally, and antigenically and with a similar mechanism of action. Both have an A and B subunit structure in which the B subunit ligand binds irreversibly to GM1 ganglioside receptor followed by internalization of the AB complex by endocytosis and subsequent proteolytic release of the catalytically active A subunit. The A subunit activates adenylate cyclase resulting in increased cyclic-AMP that stimulates chloride secretion via CFTR chloride channels and which also inhibits sodium chloride absorption. The resultant large sodium chloride driven osmotic gradient leads to water efflux in a correspondingly large volume and the clinical manifestation of purging watery diarrhea [10, 11].

With intact intestinal mucosal absorption, glucose-containing ORS increased the absorption of water and electrolytes and significantly improved survival rates during severe diarrhea. In subsequent decades, other active nutrient cotransporters such as amino acid coupled sodium absorption as well as linked ion sodium-bicarbonate and sodium-hydrogen exchange were described. During the cholera pandemic that begun in the 1960s, the National Institutes of Health (NIH) and the US agency for International Development (USAID) established two research centers in South Asia, the Pakistan Southeast Asia Treaty Organization (SEATO) Cholera Research Laboratory and forerunner of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDRB) in Dhaka, and the Johns Hopkins Center in Calcutta, India [3]. Clinical investigations by Drs. Nobert Hirschhorn and Nathaniel F. Pierce in Dhaka and Calcutta established maintenance of hydration in severe diarrhea due to *Vibrio cholera* through absorption of glucose, salt, and water [6, 10]. Hirschhorn later introduced ORT to the White River Apache Indian Reservation in the USA and showed that hydration in children was successfully restored by drinking as much as needed of the oral rehydration solution. This led to increased and wide application of ORT for children with diarrheal diseases, especially in developing countries [11–13]. As a medical resident working at SEATO Cholera Research lab, American physiologist Dr. David R. Nalin later showed that when oral glucose-electrolyte solution was given in equal volumes to diarrheal losses, there was a

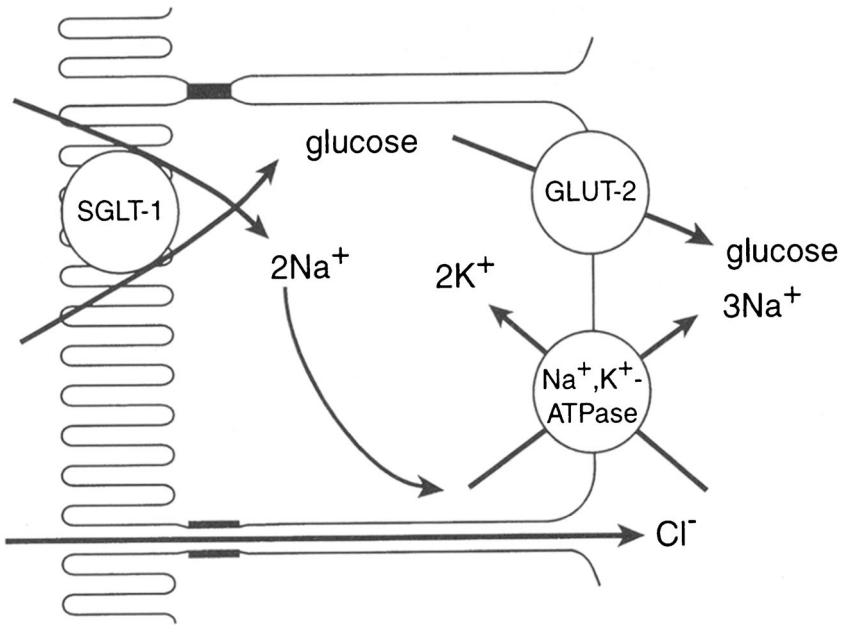

Fig. 1 Unlike the nutrient-independent sodium absorption of intestinal epithelial cells which is compromised in diarrheal disease, the sodium-glucose transporter type 1 (SGLT1) is retained and mediates transport of glucose against its concentration gradient by coupling it to sodium transport. The resultant electropositive gradient achieves electrochemical equilibrium by transport of negative chloride ions. The subsequent NaCl is electroneutral but creates an osmotic gradient leading to water absorption to achieve osmotic neutrality

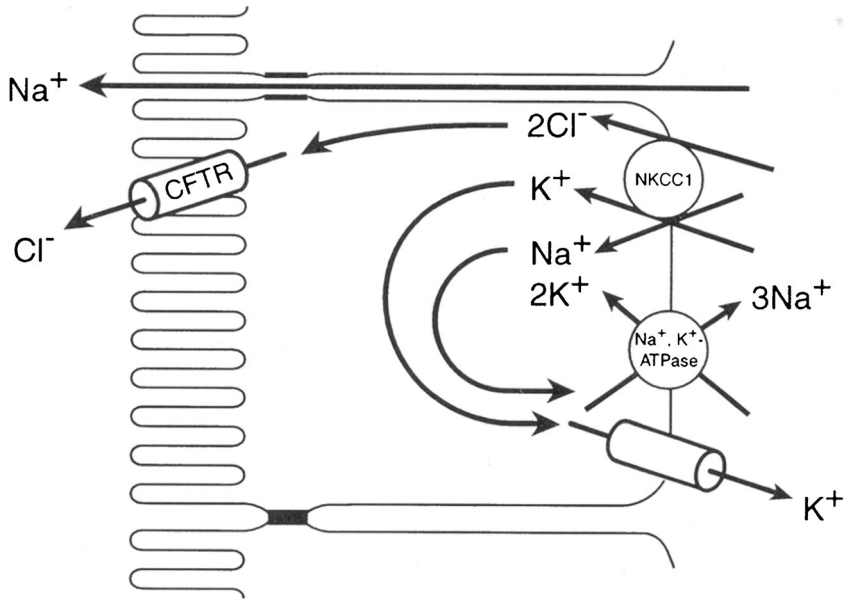

Fig. 2 Chloride excretion and fluid secretion

significant reduction in the need for IV fluid hydration [3, 6, 14] and that resulted in tenfold reduction in the mortality rate of individuals who received the oral rehydration solution compared with those that were given IV therapy [2, 4]. Successful use of ORT in refugee camp cholera outbreaks under terrible conditions during the Bangladesh Liberation War further reinforced its enormous and practical value [1••].

A sound physiologic basis and demonstration of efficacy drove further ORS research and programmatic implementation including access to treatment in community health centers, remote clinics, and home-based treatments [3]. The WHO launched the Diarrheal Disease Control Program in the late 1970s, and UNICEF produced ORS sachets that could be added to water with subsequent worldwide distribution. Advocacy was undertaken to persuade health policy makers to introduce and promote ORS [3]. In 1979, in Bangladesh, the nonprofit international development organization, BRAC, initiated field trials in which a sales taskforce was created to teach rural mothers oral rehydration therapy use at home, reinforced by radio and television broadcasts to promote oral rehydration therapy. ORS knowledge and practice in Bangladesh went from practically nil to being taken up by the majority of households and showed the potential to create a major market and that increased use of ORT. In 1985, WHO issued a new recommendation for ORS that replaced sodium bicarbonate with sodium citrate, which addressed limitations of shelf life and reduced packaging costs. In 1992, the Center for Disease Control and Prevention (CDC) issued their first recommendations on the use of ORT as the treatment of choice for diarrheal illness in children in the USA [3, 15] and Unicef has incorporated ORT as one of their low-cost interventions in developing nations to improve child survival. In addition to its remarkable impact on mortality which resulted in ORS being acclaimed as one of the greatest medical advances of the past century, ORT was also shown to decrease the length of hospitalization and cost associated with illness.

The composition of the original "standard" WHO ORS advocated as the single preparation for three decades to ensure efficacy in all causes of diarrhea including high sodium and water output such as with cholera and contained 90 mEq/L of sodium and 111 mmol/L of glucose with an osmolarity mOsm/L of 311 (Table 1) [16]. Despite proven efficacy, acceptance of oral rehydration solution by patients worldwide and particularly outside facility-based treatment centers was and remains less than optimal and even poor [16]. A constraint often cited but less well documented is that ORS did not visibly reduce the severity of diarrhea (volume of stool and duration of diarrhea), which is often perceived by patients and parents as well as health care providers to represent failure or lack of efficacy. Throughout the 1990s, additional research aimed to identify a more optimal ORS formulation based on an understanding of different mechanisms that govern

Table 1 Composition of oral rehydration solutions

	Previous standard ORS (1975)	Current standard ORS (2002)	ReSoMal
Glucose (mmol/L)	111	75	125
Sodium (mEq/L)	90	75	45
Potassium (mEq/L)	20	20	40
Chloride (mEq/L)	80	65	76
Citrate (mmol/L)	10	10	7
Osmolarity (mOsm/L)	311	245	300

ORS oral rehydration solution, *ReSoMal* rehydration solution for malnutrition

electrolyte and water transport. These have included substituting glucose with other substrates, cereals such as rice, and the addition of glycine, alanine, and glutamine, among others. While rice-based ORS is especially efficacious in cholera, none of the modified solutions had a sufficient combination of either improved efficacy, superior safety profile, cost advantage, or programmatic feasibility to replace the original WHO ORS. This changed with a major line of investigation undertaken to reduce stool output with the use of ORS focused on reduction of the osmotic load by reducing amounts of sodium or glucose (sodium and glucose ranges of 60–75 mEq/L and 75–90 mmol/L, respectively) or both. Due to inconclusive findings and methodological limitations of reduced osmolarity ORS studies, the WHO sponsored two studies, one in children with all cause acute watery diarrhea and another in adults with cholera, to bring definition to the efficacy of reduced osmolarity ORS compared with the standard 90 mEq/L ORS. The adult CHOICE trial conducted in Bangladesh observed no difference in clinical outcome with reduced vs. standard 90 mEq/L ORS; however, there were more cases of asymptomatic hyponatremia in the R-ORS group. The pediatric CHOICE study, a large multicenter trial conducted in five countries, reported no impact on the volume of stool output and illness duration but noted a 33% reduction in the need for unscheduled IV therapy, a marker of clinical efficacy [17]. This led WHO and UNICEF in 2003 to adopt a reduced osmolarity ORS (sodium 75 mEq/L, glucose 75 mmol/L, osmolarity 245 mOsm/L) as the new "standard" ORS. Although initial concerns were raised about the adequacy of a lower sodium formulation in high output diarrhea, post-marketing assessment has shown low osmolarity ORS to be suitable for most infectious diarrheal disease and remains the standard.

Rehydration of severely malnourished children with diarrhea present a distinct challenge. Diarrhea is frequent, occurring in up to nearly half a children hospitalized with severe malnutrition and confers a substantial increased risk of mortality but, unfortunately, clinical signs of dehydration cannot be reliably distinguished from those of malnutrition [18, 19]. Stereotypical fluid and electrolyte pathophysiologic sequelae occur in malnutrition including the near universal depletion in potassium, magnesium, phosphorous, among others which, if not taken into account in the rehydration of severely malnourished children with diarrhea, can have life-threatening consequences. And despite frequent concomitant mild hyponatremia, severely malnourished children including those with edematous malnutrition have an excess in intracellular and therefore total body sodium and exhibit large volume urinary sodium excretion upon initiation of nutritional rehabilitation. To address these unique needs, WHO developed a modified ORS, ReSoMal (rehydration solution for malnutrition) with lower concentration of sodium, higher potassium, and glucose and an osmolarity lower and higher than the previous and current standard reduced osmolarity ORS, respectively (Table 1). The theoretical basis for ReSoMal composition was sound and led to an assertive recommendation by WHO for its use in hospitalized severely malnourished children. Houston et al. conducted a systematic review of randomized controlled trials comparing different oral rehydration solutions in severely malnourished children with diarrhea and dehydration [17]. Stool output volume, diarrhea duration, and time to rehydration were better with standard reduced osmolarity ORS compared with the previous WHO sodium 90 mEq/L ORS. There was no difference between ReSoMal compared to the previous WHO sodium 90 mEq/L ORS and current standard WHO reduced osmolarity ORS in rehydration failure rates; however, in the two studies of ReSoMal, more children in the ReSoMal groups developed or had worsening of hyponatremia, including hyponatremic seizure. Perhaps the most likely explanation is that, unexpectedly and with rehydration with a low sodium concentration of ReSoMal, the rate of intracellular sodium transport to the extracellular blood compartment is not reliably sufficient to overcome the rate and volume of sodium urinary excretion that occurs with initiation of nutritional rehabilitation. Notably, none of the studies were performed in Africa where rates of mortality in hospitalized severely malnourished children with diarrhea are high.

ORS and ORS-like products are commercially available in many countries. For example, Pedialyte (Abbott Nutrition) is a glucose-based product with a relatively low sodium concentration (45 mEq/L) to WHO standard and reduced osmolarity ORS formulation and is suitable as a maintenance solution and appropriate for rehydration in non-severe but not high output diarrhea. The rice-based ceralyte line of solutions have a higher carbohydrate concentration that the WHO formulation. Despite common perceptions that sport drinks can be used for dehydration, liquid products such as Gatorade and juices are hyperosmolar (330–730 mOsm/L) and inappropriate as rehydration solutions for diarrhea and dehydration [20]. Compared with ORS solutions, sport drinks do not contain adequate amounts of electrolytes; sodium (23.5 mmol/L), potassium (< 1 mmol/L), chloride (17 mmol/L), and base (3 mmol/L) [21]. In addition to lower electrolyte concentration, the hyperosmolar nature of sport drinks increase fluid losses and worsen diarrheal disease.

Despite the undeniable success of ORS, barriers to broader and more consistent use of ORS persist, believed to be in part because the reduction in stool output with the standard reduced osmolarity ORS is often too subtle to be perceptible. Efforts to refine and improve ORS are ongoing, one example being the addition amylase-resistant starches including maize starch, cooked green banana, and others as short chain fatty acid precursors that stimulate Na-dependent fluid transport via apical membrane Na-H, SCFA-HCO3, and Cl-SCFA exchanges [22, 23]. In settings where diarrhea takes its greatest

toll, zinc deficiency is also widely prevalent. Several years of research has shown the addition of zinc to ORT management effectively shortens severity and duration of a diarrheal episode and often reduces the rates of subsequent diarrheal disease episodes [24]. Coordinated global initiatives have helped sensitize policy makers to ORS and zinc as key interventions for child health which facilitated national governments and local partners to implement large-scale programs that have effectively helped to reduced local barriers to access [25]. In this context, ORS usage rates increased from 35% before 2000 to 45% post-2000, which, while an improvement, still means fewer than 50% of children received correct treatment [26]. However, if scaled to full coverage, ORS has the potential to prevent more than 90% of diarrhea deaths and zinc to reduce duration of illness by 23% [27, 28]. A better understanding and means to change health care seeking behavior by caregivers and case management practices of health care providers to increase ORS usage rates are seemingly intractable challenges and remain priority research areas. Nonetheless, because of its simplicity, ease of use, and relevance in different clinical, healthcare, and community settings, ORS will continue to have substantial impact and save the lives of millions annually.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Nalin DR, Cash RA. 50 years of oral rehydration therapy: the solution is still simple. Lancet. 2018;392(10147):536–8. **This provides a great 50 years overview about the history of ORS as well as recent advancements and changes to the formulation**.
2. Guerrant RL, Carneiro-Filho BA, Dillingham RA. Cholera, diarrhea, and oral rehydration therapy: triumph and indictment. Clin Infect Dis. 2003;37(3):398–405.
3. Glass RI, Stoll BJ. Oral rehydration therapy for diarrheal diseases: a 50-year perspective. JAMA. 2018;320(9):865–6.
4. Ruxin JN. Magic bullet: the history of oral rehydration therapy. Med Hist. 1994;38(4):363–97.
5. Farthing MJ. Oral rehydration: an evolving solution. J Pediatr Gastroenterol Nutr. 2002;34(Suppl 1):S64–7.
6. Pierce NF, Banwell JG, Rupak DM, Mitra RC, Caranasos GJ, Keimowitz RI, et al. Effect of intragastric glucose-electrolyte infusion upon water and electrolyte balance in Asiatic cholera. Gastroenterology. 1968;55(3):333–43.
7. Hirschhorn N, Kinzie JL, Sachar DB, Northrup RS, Taylor JO, Ahmad SZ, et al. Decrease in net stool output in cholera during intestinal perfusion with glucose-containing solutions. N Engl J Med. 1968;279(4):176–81.
8. Sachar DB, Taylor JO, Saha JR, Phillips RA. Intestinal transmural electric potential and its response to glucose in acute and convalescent cholera. Gastroenterology. 1969;56(3):512–21.
9.• Prince EN FG. Fluid and electrolytes. In: Pediatric Nutrition in Practive. World review of nutrition and dietetics. 2nd, revised edition. ed. Basel; New York: Karger; 2015. p. 56-61. **Provides summary of electrolyte transport mechanisms, body water homeostasis, and practical aspects of clinical management of dehydration.**
10. Hirschhorn NKJ, Sachar DB, Northrup RS, Taylor JO, Ahmad SZ, Phillips RA. Decrease in net stool output in cholera during intestinal perfusion with glucose-contatinig solutions. N Engl J Med. 1968;279(4):176–81.
11. Hirschhorn N, Cash RA, Woodward WE, Spivey GH. Oral fluid therapy of Apache children with acute infectious diarrhoea. Lancet. 1972;2(7766):15–8.
12. Hirschhorn N, McCarthy BJ, Ranney B, Hirschhorn MA, Woodward ST, Lacapa A, et al. Ad libitum oral glucose-electrolyte therapy for acute diarrhea in Apache children. J Pediatr. 1973;83(4):562–71.
13. Hirschhorn N, Denny KM. Oral glucose-electrolyte therapy for diarrhea: a means to maintain or improve nutrition? Am J Clin Nutr. 1975;28(2):189–92.
14. Nalin DR, Cash RA, Islam R, Molla M, Phillips RA. Oral maintenance therapy for cholera in adults. Lancet. 1968;2(7564):370–3.
15. Duggan C, Santosham M, Glass RI. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1992;41(RR-16):1-20.
16. Fuchs GJ. A better oral rehydration solution?. An important step, but not a leap forward. BMJ. 2001;323(7304):59–60.
17. Houston KA, Gibb JG, Maitland K. Oral rehydration of malnourished children with diarrhoea and dehydration: a systematic review. Wellcome Open Res. 2017;2:66.
18. Talbert A, Thuo N, Karisa J, Chesaro C, Ohuma E, Ignas J, et al. Diarrhoea complicating severe acute malnutrition in Kenyan children: a prospective descriptive study of risk factors and outcome. PLoS One. 2012;7(6):e38321.
19. World Health Organization. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: World Health Organization; 1999. vi, 60 p. p.
20. Matarese LE, Steiger E. Dietary and medical management of short bowel syndrome in adult patients. J Clin Gastroenterol. 2006;40(Suppl 2):S85–93.
21. Rao SS, Summers RW, Rao GR, Ramana S, Devi U, Zimmerman B, et al. Oral rehydration for viral gastroenteritis in adults: a randomized, controlled trial of 3 solutions. JPEN J Parenter Enteral Nutr. 2006;30(5):433–9.
22. Binder HJ. Role of colonic short-chain fatty acid transport in diarrhea. Annu Rev Physiol. 2010;72:297–313.
23. Rabbani GH, Teka T, Zaman B, Majid N, Khatun M, Fuchs GJ. Clinical studies in persistent diarrhea: dietary management with green banana or pectin in Bangladeshi children. Gastroenterology. 2001;121(3):554–60.
24. Mazumder S, Taneja S, Bhandari N, Dube B, Agarwal RC, Mahalanabis D, et al. Effectiveness of zinc supplementation plus oral rehydration salts for diarrhoea in infants aged less than 6 months in Haryana state. India Bull World Health Organ. 2010;88(10):754–60.
25. UNICEF/WHO. Diarrhoea: why children are still dying and what can be done. 2009 2009:68.

26. Sreeramareddy CT, Low YP, Forsberg BC. Slow progress in diarrhea case management in low and middle income countries: evidence from cross-sectional national surveys, 1985-2012. BMC Pediatr. 2017;17(1):83.
27. Sabot O, Schroder K, Yamey G, Montagu D. Scaling up oral rehydration salts and zinc for the treatment of diarrhoea. BMJ. 2012;344:e940.
28. Munos MK, Walker CL, Black RE. The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. Int J Epidemiol. 2010;39(Suppl 1):i75–87.