HK J Paediatr (new series) 2000;**5**:52-60

Occasional Survey

Fluid and Dietary Management of Acute Infantile Diarrhoea

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Abstract Oral rehydration solution is not widely used in Hong Kong for treatment of acute diarrhoea despite its well proven efficacy. Hypotonic oral rehydration solutions with osmolarity of 200 to 250 mmol/L and containing sodium of 60 mmol/L are safe in developed countries with the added effects of decreasing stool output and the duration of diarrhoea. Rice-based oral rehydration solutions are well tolerated in infants younger than 6 months of age. More evidence is required to justify its replacement of the glucose-based hypotonic oral rehydration solutions. Rehydration should be achieved within 4 hours. Breast feeding should be continued in acute diarrhoea. Resumption of lactose-containing normal diet immediately after rehydration does not result in worsening of diarrhoea, increased lactose intolerance and prolongation of the duration of diarrhoea but results in significantly better weight gain. Routine dilution of milk and routine use of lactose-free milk are unnecessary in most cases. Anti-diarrhoeal agents should not be used to treat acute diarrhoea in children.

Key words Acute infantile diarrhoea; Oral rehydration solutions; Early refeeding; Management guidelines

Introduction

Acute diarrhoea is a principal cause of morbidity and mortality among children in developing countries. The prompt and correct use of an oral glucose electrolyte solution, developed and advocated by the World Health Organisation (WHO) and UNICEF, has revolutionized the management of acute diarrhoea. Yet these solutions were widely underused in diarrhoeal episodes, partly due to the inability of the standard WHO solution to decrease stool volume and to shorten the duration of diarrhoea. Improvements in the formulations of oral rehydration therapy have been made in the past 20 years. This article aims to review the rationales and clinical efficacies of different types of oral rehydration solutions. The rationales for early refeeding is also reviewed. Management guidelines as suggested by the American Academy of Paediatrics (AAP) and other reviews will be summarised.

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Received March 17, 1999

Physiological Basis of Oral Rehydration Therapy (ORT)

Transport of fluid and electrolytes across the intestinal epithelium can occur by solvent drag, passive processes or secondary active processes. The solvent drag process appears to be important in the overall in vivo transport of nutrients; it involves the transport of solutes during movement of water while passive processes occur in response to electrochemical gradients.[1] Solvent drag and passive processes can occur through a transcellular or a paracellular pathway. The paracellular pathway is the dominant route for passive transepithelial solute flow in the small intestine. The resistance of the tight junctions at the apical poles of the paracellular pathway decreases markedly when glucose is added to the luminal side of the epithelial cells, and the paracellular space appears to undergo dilatation to accommodate the transport of nutrients. Secondary active processes only occur in transcellular movement which requires energy, shows saturation kinetics with carriers and is efficient at low luminal concentration (Figure 1).

Sodium (Na) absorption in the intestine can occur through one of 3 mechanisms: solute-coupled sodium absorption, electroneutral sodium-chloride absorption and electrogenic sodium absorption. Solute-coupled sodium absorption is an active and carrier mediated process. The

NHE-2,3 (Na^+/H^+ Exchangers)
AE-1 (Anion Transport Protein)
GLUT2 (Glucose Trasporter-2)
SGLT1 (Sodium-dependent Glucose Transporter-1)

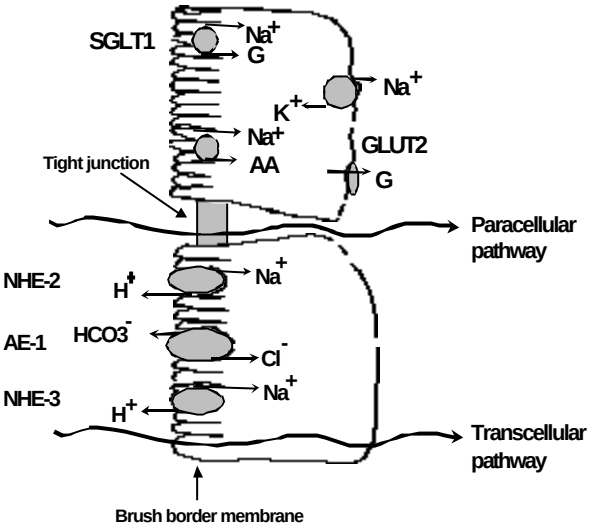

Figure 1 Electroneural and solute-coupled Na^+ absorption across the luminal membrane of enterocytes

Na^+-glucose cotransporter present in the luminal membrane of enterocytes was termed Sodium-dependent Glucose Transporter-1 (SGLT1). The stoichiometric coupling ratio of Na^+ to glucose by this transporter is 2:1. It has a role not only in dietary glucose absorption but also in sodium and water absorption. The transport of glucose across the basolateral membrane into the blood is mediated by a facilitated glucose transporter, Glucose Transporter-2 (GLUT2). The rationale for the administration of oral electrolyte solutions containing sodium and glucose is based on the fact that Na^+-glucose coupled transport stimulates water absorption by solvent drag. This mechanism remains intact in patients with diarrhoeal disorders with increased mediators of secretion, as in cholera and rotavirus infections.[2,3] The Oral Rehydration Solution (ORS) recommended by WHO should therefore be an effective rehydration agent; as the sodium and glucose in the ORS would potentiate transport of water and electrolytes across the intestinal epithelium.

Efficacy of Standard WHO-Oral Rehydration Solution (ORS)

Intravenous fluid was first used by Latta in 1832 to treat diarrhoea induced by cholera. It was not until the 1950s that Harrison reported his first experiences of success with ORT.[4] In the 1960s, the coupled transport of glucose and sodium was described, providing the scientific basis for ORT.[5,6] In 1973, a cholera epidemic in Bangladesh was effectively treated with ORT [7] and in 1985 the WHO adopted ORT for rehydration for diarrhoea and promoted its application throughout the world. In an editorial in the Lancet in 1978, the use of ORT was described as "potentially the most important medical advance in this century".[8]

The standard WHO-ORS can successfully rehydrate 90% of patients with dehydration due to acute diarrhoea.[9] However it does not reduce the rate of stool loss or the duration of the illness, which are the main concerns of parents and many healthcare workers.[10,11] In 1996, Gavin conducted a meta-analysis of 13 randomised control trials comparing the safety and efficacy of ORT with intravenous rehydration treatment in developed countries among well-nourished young children with gastroenteritis.[12] The overall failure rate of ORT was only 3.6% (Table 1) and the risk of iatrogenic hypernatraemia or hyponatraemia was not increased compared to intravenous therapy. Of the six studies with intravenous arms, ORT was associated with slightly more favourable results in terms of weight gain and the duration of diarrhoea. However, stool frequency and stool volume were higher in the ORT group, further supporting the fact that ORT has no effect on stool volume, frequency of stools and probably, duration of diarrhoea also. Therefore subsequent efforts were focused on improving these functions of ORT.

Hypotonic Solutions

The inability of the WHO-ORS to reduce stool volume may be due to its slight hypertonicity, combined with incomplete absorption of glucose in some children, resulting in osmotic diarrhoea. In recent years, several

Table 1 Meta-analysis of treatment failure rates of oral rehydration therapy from 13 randomized, controlled trials

	No. of studies	No. of case	(Weighted Proportion±SE) Failure rate
Trials with IV arms	6	193	5.7±2.0
Trials without IV arms	7	610	3.0±1.2
Overall	13	803	3.6±1.1

Treatment failure is defined as the persistence or recurrence of signs of dehydration beyond 24 hours of oral rehydration therapy and other clinical indications requiring the need to revert to intravenous therapy (IV).
Modified from Gavin N, Pediatrics 1996;98:45-51 [12]

investigators have proposed that an ORS solution made hypotonic by reducing both the glucose and sodium concentration may be more absorption efficient.[13-16] Oral rehydration solutions containing 60 mmol/L sodium have been shown to be as effective clinically as higher sodium ORSs; and they are rarely associated with disturbances of the plasma sodium concentration.[17] In developed countries where cholera infections are uncommon and most young children well-nourished, ORSs of lower sodium concentration have been recommended in both the rehydration and the maintenance phases to avoid hypernatraemia.

Scientific Basis for Hypo-osmolar Solutions

In the past, the glucose to sodium ratio in ORS was about 2:1. This was based on the stoichiometric coupling ratio of SGLT1 and the result of an in vivo perfusion system on rat jejunum that showed maximum influx of water and sodium with a solution containing 60 mmol/L of sodium and 111 mmol/l of glucose.[13] Subsequent studies using animal models and human perfusion techniques showed that optimal water absorption can be obtained using a hypotonic solution with sodium concentration of 50-60 mmol/l and glucose concentration of 50-100 mmol/l.[19,20] Since a high carbohydrate content of the rehydration solutions may lead to osmotic diarrhoea due to non-absorbed carbohydrates, especially in rotavirus infections, the AAP and WHO subsequently recommended the use of solutions with a glucose to sodium ratio of less than 2.0:1 and 1.4:1 respectively.[21]

A study with rat perfusion models was reported comparing a hypotonic ORS with sodium of 60 mmol/l, glucose of 90 mmol/l and an osmolarity of 240 mosmol/l with the Standard United Kingdom British National Formulary and the WHO-ORS, both with much higher osmolarity and glucose concentration.[15] The hypotonic ORS induced net water absorption in *cholera* toxin treated and rotavirus infected secreting rat small intestines but did not promote net sodium absorption in either. These effects of hypotonic ORS are probably the result of passive water absorption induced by the osmotic gradient produced with this solution. Subsequent studies in animal models and human volunteers have shown that osmolarity, rather than sodium concentration and the sodium-glucose ratio, may be the most critical determinant of intestinal absorption of an ORS.[19,22,23] Water absorption from ORS with osmolarity between 200 and 250 mosmol/l is better than that from solutions isotonic with plasma.[15,19,20]

Clinical Efficacies

A preliminary clinical study with hypotonic ORS has indicated that it is effective for rehydration and reduction of stool volume compared with an established slightly hypertonic ORS.[24] In an open study in Finland, the use of low osmolarity ORS (osmolarity 224 mosmol/l and glucose 84 mmol/l) was associated with a decrease in stool volumes and the duration of diarrhoea.[25] The beneficial effects on the clinical course of acute diarrhoea were confirmed in a double blinded multicenter study by the International Study Group on Reduced-Osmolarity ORS in 4 developing countries.[26] In this study, the use of a low-osmolarity ORS with osmolarity of 224 mosmol/l, glucose of 84 mmol/l and sodium of 60 mmol/l was compared to that of standard WHO-ORS with osmolarity of 311 mosmol/l. Treatment with the reduced-osmolarity ORS resulted in deceased stool output (39%), decreased ORS intake (18%), decreased duration of diarrhoea (22%) and increased urine output. However, there was no difference in the serum sodium concentrations. Other studies with hypotonic ORSs of 224 to 249 mosmol/l have also confirmed these beneficial effects.[16,17,28] The ability of low sodium ORSs to repair sodium deficits probably results from effective sodium salvage by the terminal ileum and colon.

Based on these data, the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) recommended in 1992 the use of an ORS solution containing 60 mmol/l sodium, 74 to 111 mmol/l glucose with an osmolarity between 200 and 250 mosmol/l.[29]

Cereal-based ORS

Another way to improve the efficacy of ORT is to replace glucose with organic solutes such as starches to reduce the osmolarity and to increase the co-transport molecules for the coupled transport of sodium.[30] A variety of starches has been used successfully including rice, wheat, maize and sorghum.[31] Most experience has been with rice based solutions containing 50-80 g rice for each litre of water.[32-35]

Scientific Basis for Rice-based ORS

Rice starch is not a pure carbohydrate. The apparent superiority of rice-based ORS has been attributed to its capacity to release more glucose from rice starch at the brush border than is present in glucose-based ORS, facilitating greater coupled transport with sodium while maintaining low osmolarity.[30] In addition to glucose polymers, it also provides amino acids and short chain peptides that can act as co-transporters to enhance sodium and water absorption without incurring an osmotic penalty in the gut.[36,37] Other possible mechanisms included kinetic advantage of oligosaccharide over glucose monomers and low osmolarity.[38-40] The increased effectiveness of starch

was supported by in vivo perfusion studies in rats where a short chain glucose polymer of rice was more effective than D-glucose in correcting abnormal water and ion secretion induced by dibutyryl cyclic AMP.[41]

One of the major concerns for the use of rice-based ORS is that young infants have low levels of pancreatic amylase which may result in incomplete digestion of starch.[42] However, other studies have shown that infants as young as 1 month can digest and absorb substantial amount of rice possibly due to amylases in the saliva and breast milk. Brush border disaccharidases such as glycoamylase are plentiful at birth [43] and are also well preserved during intestinal inflammation compared with other disaccharidases.[42] In addition, bacterial fermentation in the colon may contribute an important part in carbohydrate digestion and absorption by converting malabsorbed sugars to hydrogen gas and short chain fatty acids.

Clinical Efficacies of Rice-based ORS

Clinical trials give conflicting results. Some studies showed that an ORS containing cooked rice powder (50-80 gm/l) in place of the usual glucose (20 gm/l) substantially reduced the rate of stool loss and shortened the duration of the illness in acute diarrhoea [18,31,33,44,45] while other studies reported no significant benefit.[46,47]

In a meta-analysis of 13 randomised controlled trials involving more than 1300 children and adults, treatment with rice-based ORS resulted in significantly lower stool volume (36%) in the first 24 hours as compared with WHO-ORS.[48] In addition, it also resulted in a shorter duration of diarrhoea. However, this reduction in stool volume was less impressive in children with non-cholera diarrhoea (18%). In another randomised controlled trial in Australia involving 100 children under the age of 5 years, 40% of which were caused by rotavirus infections, rice-based ORS resulted in significant decrease of stool output, duration of diarrhoea, recovery time and the length of stay as compared to a hypotonic glucose-based ORS.[49]

In another large randomised controlled trial specifically designed to compare the relative efficacies of rice-based ORS and glucose-based ORS that were followed by nutritious cereal based weaning food immediately after rehydration, there was no difference in stool volume, volume of ORS consumed, duration of rehydration and weight gain in the rehydration phase.[50] After rehydration, treatment with glucose-based ORS was associated with lower stool output and shorter duration of diarrhoea. The study concluded that when adequate nutritious diet was provided early, rice-based ORS is no more effective than treatment with glucose-based ORS.

The efficacy in infants less than 6 months old was confirmed in a small randomised study in which rice-based ORS resulted in decrease in stool output and ORS consumption as compared to WHO-ORS.[51]

Nearly all these studies were characterized by highly heterogenous patient groupings with different causes of diarrhoea. In addition, most studies were comparing the efficacy of rice-based ORS with the hypertonic WHO-ORS, rather than with hypotonic glucose-based ORS. The relative variability present in these studies, and in some instances, the lack of sufficient subjects to support the conclusions drawn made definite conclusion difficult.[49] In view of the fact that preparation of rice-based ORS is more tedious,[48] more evidences are preferrable to justify its routine use in place of the glucose-based hypotonic ORS. We have also introduced a low sodium rice-based ORS to our hospital since 1984. This rice-based ORS was more culturally receptive and it was found to be equally effective in its therapeutic effects for diarrhoeal children compared to a similar electrolyte solution containing 20 gm/l of glucose.[18]

Nutrients other than glucose have been used with success for sodium cotransport, including sucrose, alanine, glycine and glutamine. These ORSs do not seem to provide any additional therapeutic advantage over standard glucose-based ORS solutions in the treatment of dehydration.

Nutritional Management - Early Refeeding

Conventional Thinking of Delayed Refeeding

Until the 1970s, the incidence of lactose intolerance was reported to be as high as 50 to 70% in both the developed and developing countries.[52] This was especially common in very young infants and in malnourished children. To avoid the potential consequences of lactose malabsorption, young children with acute diarrhoea were usually starved for 24 to 48 hours in the belief that unabsorbed food substances would create an osmotic load that would lead to electrolyte and water losses. Delayed refeeding was also thought to prevent sensitisation to cow's milk antigens when permeability to marcomolecules in the small intestine may be enhanced during infection.[53] This fasting period was followed by a gradual increase or regrading in the concentration of formula.[54]

Recent Evidences

The counterpoint to this argument is the deleterious effect of delayed refeeding on the overall nutritional status, especially in developing countries where children may have quite a few episodes of diarrhoea per year. Delayed feeding may contribute to substantial atrophy of the structure and function in the small intestine while early refeeding may have positive effects on mucosal growth

by enhancing enterocyte regeneration and promoting recovery of brush border membrane disaccharidases.[55] A recent study also showed that nutrition may actually decrease the intestinal permeability changes that is induced by infection.[56]

Studies have shown that continuation of breast feeding during acute diarrhoea actually reduces the severity and duration of diarrhoea.[57,58] It has now been universally accepted as the standard practice. Several studies over the past 15 years have shown that there is no need for slow regrading and that full feeding appropriate for age is well tolerated with no adverse effects.[59-67] However, the presence of risk factors including young age and severe diarrhoea may caution against early refeeding.[68]

In a meta-analysis of 29 randomised controlled trials involving more than 2000 children, treatment outcome variables were compared for children treated with: (1) either lactose-containing milks or lactose-free products and (2) either undiluted or diluted lactose-containing milks.[69] Treatment failure was not increased in children treated with lactose-containing diets if they were mildly to moderately dehydrated and were treated with appropriate rehydration protocols with ORS (Figure 2). When other solid food was provided in addition to milk, the inclusion of lactose did not affect the duration of illness. Treatment failure was only more likely in the lactose group in children who were malnourished or severely dehydrated. Early introduction of undiluted lactose-containing milk was associated with no difference in the duration of diarrhoea but a slight but insignificant increase in stool output (Table 2). There was better weight gain in the group with undiluted milk. The authors have therefore concluded that routine dilution of milk and routine use of lactose-free milk are unnecessary in most cases, especially when ORT and early feeding with solid foods form the basic approach to the clinical management of diarrhoea in infants and children.

In a multicenter European study conducted by the

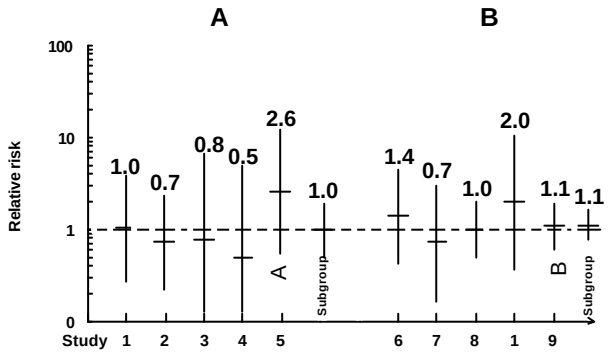

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Figure 2 Relative risk of treatment failure in patients with mild dehydration with: (A) lactose-containing diet vs lactose free diet; (B) undiluted milk diet vs diluted milk diet.

Table 2 Pooled data for stool frequency, stool output and duration of diarrhoea of patients receiving either undiluted lactose-containing milk or the same milk at reduced concentration or introduced later during therapy

	Dietary Group					
	Undiluted		Diluted/Delayed			
	mean ± SD	n	mean ± SD	n	d*	p
Stool frequency (no. of bowel movements per day)	7.3 ± 6.3	240	7.0 ± 6.6	240	0.18	0.046
Stool output (gm/day or gm/kg/day)		137		135	0.22	0.056
Duration of diarrhoea (hours)	72 ± 39	437	72 ± 40	439	0.02	0.45

d* = the standardized difference between treatment groups

Modified from Brown KH, Pediatrics 1994;93:17-27[69] (with permission of the American Academy of Pediatrics)

Working Group on Acute Diarrhoea, ESPGAN, complete resumption of normal diet including lactose containing formula after 4 hours of rehydration with ORS solution did not result in worsening of diarrhoea, increased lactose intolerance or prolongation of the duration of diarrhoea, but resulted in significantly better weight gain compared to babies fed ORS only within the first 24 hours.[70] In this study, the incidence of lactose intolerance was only about 5% at entry and nil on day 5 and day 14, even though vast majority of them has rotavirus infections. Indeed this low incidence of lactose intolerance after acute diarrhoea has also been observed.[52] On the bases of these data, restriction of lactose-containing foods for the vast majority of children in developed countries with gastroenteritis does not appear to be justified. ESPGAN has therefore recommended that normal feeds should be reintroduced immediately after rehydration with ORS solutions while breast feeding may be continued throughout rehydration and the maintenance phases of treatment. Lactose free formula is rarely necessary. If persistent diarrhoea occurred after reintroduction of milk, the stool should be tested for pH and reducing substance. Lactose-free formula should be given if the stool pH is less than 5 and contains more than 0.5% reducing substances.[71]

Questions have been raised to see if continued feeding is safe in infants under 6 months of age and whether malnourished children respond adversely to early refeeding. In a study conducted in Latin America in babies under 6 months of age, infants randomly assigned to receive full strength cow's milk formula immediately after rehydration did not have more treatment failures, higher stool outputs, or longer lasting diarrhoea than those regraded to full strength over 48 hours.[72] In addition, reducing substances in stools were common both in treatment successes and in failures, indicating that any decision to change to lactose-free formula should not be ruled by slavish adherence to the presence of reducing substances in the faeces.

The Local Scene

How are we treating acute childhood diarrhoea in Hong Kong? In a recent study looking at the management practice by primary care physicians and parents perception of appropriate treatment of acute diarrhoea in Hong Kong, misconception prevails both among the professionals and laypeople.[73] ORS was only recommended by 11% of doctors. Eleven percent of parents were advised to stop milk feeds temporarily while another 11 % were advised to change to lactose-free formula. One mother who has been exclusively breast-feeding was advised to stop breast feeding. Over 90% of practitioners prescribed more than one drug and the median number of drugs prescribed was 3.0, including antidiarrhoeal agents and antibiotics. Doctor shopping was common and up to 73 % of parents had been seen by more than one practitioners prior to admission. Only 30% of caregivers regarded replacement of fluid loss as important, while 41% and 26% regarded control of fever and stopping diarrhoea as most important. Only 50% considered it important to continue solid foods and there was also a strong belief that drugs should be given.

Management Guildelines

In 1996, the American Academy of Pediatrics (AAP) published the practice parameter on the management of acute gastroenteritis in young children after a comprehensive search and analysis of the medical literature with expert consensus opinion.[74] Management guidelines for acute gastroenteritis was also published in a review article by Murphy in 1998, basing on a systematic review of published research.[75] Their recommendations are very similar and are summarised as below:

Electrolyte Measurement

Most episodes of dehydration caused by diarrhoea are isonatraemic, and serum electrolyte determination are unnecessary, except in moderately dehydrated children whose histories and physical findings are inconsistent with straightforward diarrhoea and in all severely dehydrated children.

Recommendations on Fluid Management

1. Most children with vomiting and dehydration can be treated with ORT. The key to therapy is to administer small volumes frequently.
2. An ORS containing sodium 60 mmol/L, glucose 90 mmol/L, potassium 20 mmol/L, and citrate 10 mmol/L with an low osmolarity of 240 mmol/L is safe and effective for the prevention and treatment of dehydration in developed countries. The compositions of commonly used ORSs are listed in Table 3.
3. ORS is the first choice of therapy in children with mild to moderate dehydration.
4. Rehydration should normally be completed over a three to four hour period.
   (a) Mild dehydration (3-5%): 50 ml/kg
   (b) Moderate dehydration (5-10%): 100 ml/kg
   (c) Severe dehydration (10+%): 100-150 ml/kg
   (d) Severe dehydration with shock: Bolus intravenous fluid 20 ml/kg over 1 hour
   Rehydrate as in (c)
5. Reassess hydration and tolerance of fluid regularly.

Table 3 Compositions of commonly used oral rehydration solutions

Solute (mmol/L)	WHO	BNF	ESPGAN	Pedialyte	GES 45	Diocalm Junior	QMH
Sodium	90	35	60	45	45	60	50
Glucose	111	200	74-111	25	160	111	50 *
Potassium	20	20	20	20	25	20	20
Bicarbonate	--	18	--	--	25	--	--
Citrate	10	--	10	30	--	10	10
Chloride	80	35		35	45	50	40
Osmolarity	311	310	200-250		300		

QMH = Queen Mary Hospital; *grams of rice powder / L solution

6. In hypernatraemic dehydration, ORT is safer than intravenous rehydration.
   Use "slow ORT", aiming to complete rehydration over 12 hours, and monitor serum sodium to avoid rapid reduction.
7. Replace ongoing loss by ORT at 10 ml/kg for each stool.

Recommendations on Nutritional Management

1. Breast feeding should continue through rehydration and maintenance phases of treatment.
2. Lactose free formula and dilute milk is not indicated in most children.
3. Formula feeds and normal diet should be restarted after completion of rehydration.
4. If there is persistent diarrhoea after reintroduction of feeds, evidence for lactose intolerance including stool pH and presence of reducing substances should be sought. Lactose free formula should then be considered.

Recommendations Regarding Pharmacotherapy

- Infants and children should not be treated with antidiarrhoeal agents.
- Most bacterial gastroenteritis does not require or benefit from antibiotic treatment.

1. Antidiarrhoeal agents

Many antidiarrhoeal agents were used in the treatment of acute gastroenteritis with little evidence of benefit, especially in children. Many of the agents have systemic toxic effects that are augmented in infants and children and most are not approved for children younger than 2 or 3 years. The AAP recommended that as a general rule, pharmacologic agents should not be used to treat acute diarrhoea.

2. Antimicrobial agents

Most bacterial gastroenteritis does not require or benefit from antibiotic treatment. Antibiotics are indicated in gastroenteritis caused by *Shigella, cholera, Enteroinvasive E coli and Clostridium difficile*. Therapy for Salmonella gastroenteritis is reserved for the infants younger than 3-6 months of age, in immunocompromised patients, and in those who are systemically ill. *Campylobacter* may be treated with erythromycin in those patients with severe or prolonged illness or to decrease the duration of shedding. *Enter-toxigenic E coli*-related diarrhoea, the chief cause of traveller's diarrhoea and diarrhoea in children in developing countries, will respond to trimethoprim/ sulfamethoxazole in most cases, although milder cases can be managed with fluid therapy alone.[76]

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