Diarrhoeal Disease

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Summary

1. Use oral rehydration solution (ORS) for mild to moderate dehydration (sugar or rice-based).
2. Use rapid IV rehydration over four hours with Ringer's lactate (Hartmann's solution) for moderate-severe dehydration.
3. Start re-feeding early with appropriate feeds (avoid prolonged fasting).
4. Severe dehydration, acidosis and hypokalaemia are complications of gut damage, leading to lactose intolerance in Aboriginal children.
5. Oral tilactase may help (Lact-easy 10 drops with each feed) for breastfed infants with positive stool reducing substances, or if you suspect lactose intolerance.
   [Ed: This recommendation was not supported by the editorial committee due to limited evidence of effectiveness in community settings and an expectation that it would be impractical.]
6. Avoid inappropriate use of antibiotics, anti-diarrhoeal medications and nasogastric tubes.
7. Zinc and vitamin A supplements are recommended for persistent diarrhoea and malnutrition.

Prevalence

Between 1991 and 1995, NT Indigenous infants (aged under one year of age) had an infant mortality rate of 22.5 per 1000 live births, which is over three times the average of the NT non-Indigenous population.[1] The overall annual hospitalisation rate for Aboriginal children in the Top End is extremely high, at about 1.4 admissions per child under two years. With regard to diarrhoeal disease alone, Aboriginal children have a much higher rate of hospitalisation than non-Aboriginal children. Between 1993 and 1997, the annual diarrhoeal admissions rate for Top End Aboriginal infants was 334 per 1000 compared to 20 per 1000 for non-Aboriginal infants, a 16-fold higher rate. For children one to four years old, the equivalent rates were 119 per 1000 for Aboriginal children and 10 per 1000 for non-Aboriginal children, or about a 12-fold higher admission rate.[2] These admission rates in Aboriginal children may have been falling over the last decade (e.g. for children 0–2 years of age, the rate fell from 4063 per 18 034 population in 1986–88 to 2301 per 13 957 in 1997–98), although this apparent decrease may be due to changes and errors in coding (Alan Ruben,

pers. comm.). There has been no decrease in health centre visits for diarrhoea over that time.[3] In addition to the high diarrhoeal admissions rates Aboriginal children also have a longer length of stay for diarrhoeal disease, which averages about nine days compared to three days in non-Aboriginal children.

Aboriginal children hospitalised for diarrhoea also have high rates of co-morbidities, including lower respiratory infections (e.g. pneumonia, bronchiolitis) (24%) skin diseases (scabies, pyoderma) (27%), chronic suppurative otitis media (25%), urinary tract infections (15%), and bacteraemia (5%).[4,5] This is a reflection of the generally higher burden of disease in Aboriginal children, including very high rates of bacterial colonisation of the upper respiratory and GI tracts.

Aboriginal children hospitalised with diarrhoea have rates of severe complication which are much higher than non-Aboriginal children, and include moderate to severe dehydration (affecting 67% of RDH admissions), acidosis (61%) and hypokalaemia (65%).[5] These complications are due to severe intestinal mucosal damage as reflected in high intestinal permeability ratios, with the loss of brush border lactase exacerbating osmotic diarrhoea when there is a high lactose diet, such as in breast milk. Lactose malabsorption was documented in 42% and lactose intolerance (positive stool reducing substances) in 30% of diarrhoeal cases in hospitalised children who are breastfed.[5]

A randomised trial in Darwin showed that a low osmolality lactose-free milk formula (De-Lact) resulted in less diarrhoea and more weight gain than O-Lac or Alfaré formulas.[6] There is only anecdotal evidence that oral tilactase (Lact-Easy drops) with each breast feed reduces the severity of lactose intolerance in breastfed children with acute gastroenteritis. The main problem with its effectiveness is the short time of exposure of the enzyme to breast milk lactose when given to infants after breastfeeding. Ideally, breast milk should be expressed, the drops added, wait 30 minutes for the lactose to be hydrolysed and then fed to the infant.

The most frequently isolated enteric pathogens in Aboriginal children hospitalised with diarrhoea in Darwin are enteroaggregative E. coli (EAggEC) (29%), rotavirus (27%), enteropathogenic E. coli (EPEC) (17%), Salmonella species (11%), Cryptosporidium (7%) and Strongyloides (7%). Note that the prevalence of intestinal worms, such as hookworm and dwarf tapeworm (H. nana), was very low, and they do not cause diarrhoea. Whipworm (Trichuris) was found in about 3% of children and did not cause either diarrhoea or bowel damage. We documented giardiasis in only 6.8% of controls and 3% of diarrhoeal cases, which may be an underestimate due to the lack of sensitivity of stool microscopy, but giardiasis did not make a major contribution to either severe disease or abnormal permeability in our diarrhoeal subjects.[7] It may be contributing to the tropical enteropathy in healthy Aboriginal children but is not a major cause of poor growth.[8–10]

The importance of intestinal parasites (e.g. hookworm, whipworm) on Aboriginal child health is often exaggerated, and published studies[11–15] are not representative of the current situation in view of the widespread use of albendazole in many communities. However, Strongyloides is still an important cause of acute diarrhoea[5,16], but other intestinal parasites have little public health importance.

Stool microbiology is often requested in Aboriginal children with diarrhoea. However, its usefulness is often questioned, because it seems not to affect clinical decision-making and E. coli probes are not available routinely. The addition of diagnostic tests for diarrheagenic E. coli to

standard stool microbiological testing increased the rate of specific diagnosis from 53% to 75% in Aboriginal children at Royal Darwin Hospital. 52% (66/127) of Aboriginal diarrhoeal admissions had a pathogenic E. coli species isolated, although multiple pathogens were isolated from 34% of children and no organism from 25%.[7]

The Infectious Diseases Guidelines of America recommend selective testing of stool microbiology in children hospitalised with moderate to severe diarrhoea (length of stay >3 days) for both individual patient care and public health purposes, particularly for E. coli 0157 due to its role in haemolytic uraemic syndrome.[17] In view of these findings, we would argue that E. coli probes on stool should be a funded routine investigation in hospitalised Aboriginal children in northern and Central Australia. After all, if E. coli species were associated with over half of diarrhoea in southern Australia, it would now be a routine investigation like rotavirus.

Out of the common enteric pathogens, rotavirus causes transient but severe intestinal mucosal damage associated with acidosis and lactose intolerance. Cryptosporidium causes severe and prolonged mucosal damage whereas Strongyloides is more likely to occur in malnourished children, but both Cryptosporidium and Strongyloides cause hypokalaemia, which is associated with high levels of nitric oxide production, indicative of gut inflammation.[16] The organisms associated with the most severe intestinal mucosal damage on admission are Cryptosporidium, EAggEC and rotavirus, but only Cryptosporidium causes continuing mucosal damage after clinical recovery.[5]

Healthy Aboriginal children without diarrhoea have higher permeability ratios than non-Aboriginal children, indicating the presence of tropical-environmental enteropathy syndrome.[4,5] Overseas studies have shown that this is related to overcrowded living conditions and poor hygiene, with bacterial contamination of food and water.[18] It has been found in poor developing country settings to contribute to almost half of the failure to thrive from malabsorption, particularly of carbohydrates.[19,20] Poor environmental conditions have also been documented in tropical Australian Aboriginal communities.[21] Failure to thrive, faltering growth, stunting and nutritional microcephaly are common problems in Aboriginal community children.[22,23] Improving hygiene and living conditions would be likely to reduce the transmission of enteric pathogens and improve the underlying mucosal damage. This would reduce the severity of diarrhoeal disease in communities so that it could be managed with oral rehydration without the need for referral to hospital. It would also reduce the nutritional consequences of carbohydrate malabsorption.

Diagnosis

As a symptom, diarrhoea is a more reliable indicator of acute gastroenteritis than most other symptoms in children, such as cough, fever, shortness of breath or wheeze for respiratory illnesses (pneumonia, asthma). The diagnosis of acute gastroenteritis is even more specific if the stools are watery and green with >3/day and the illness lasts for at least 2–3 days. However, diarrhoea may be a non-specific symptom of other non-enteric infections, such as urinary tract infections in infancy and upper respiratory tract infections. Severe vomiting — which is bile-stained or projectile — and severe abdominal pain are unusual in acute gastroenteritis, so need to have surgical conditions considered, especially

in infancy (e.g. intestinal obstruction, pyloric stenosis, intussusception).[24]

Dysentery is defined as the presence of blood and mucus in diarrhoeal stools. Compared to most developing country settings, dysentery is much less common among Aboriginal community children, since it accounts for <5% of diarrhoeal cases in Darwin. The most likely cause of dysentery is Shigella which can cause outbreaks of severe bloody diarrhoea. Haemolytic-uraemic syndrome (HUS) is caused by a shiga-like toxin produced by enterohaemorrhagic E. coli (EHEC). This results in a haemolytic anaemia (typical blood film appearance) and acute renal failure. It causes severe disease but is fortunately rare, although outbreaks can occur. Antibiotic treatment of diarrhoeal disease may cause harm, since it makes HUS more likely with EHEC and prolongs the duration of carriage of Salmonella.[17]

Assessment of dehydration

The risk factors for dehydration are: 1) young age due to the increased surface area to body volume ratio, resulting in increased insensible fluid loss; 2) a milk diet, due to the risk of osmotic diarrhoea and the large protein load, which causes a high renal solute load; and 3) bottle feeding rather than breastfeeding.[25] Clinical assessment of dehydration has low sensitivity, and signs only become present with moderate to severe dehydration (?5%). A Melbourne study found that poor capillary return was the most reliable clinical sign of dehydration.[26] An American study found that the four signs which were the best predictors of dehydration were: a capillary refill time >2 seconds; absent tears; dry mucous membranes; and ill general appearance.[27] Capillary refill time is a useful sign of dehydration but can be affected by fever, ambient temperature (air conditioning) and age.[28] Other studies have found laboratory tests generally insensitive in assessing hydration, but bicarbonate, urea, creatinine and uric acid have been the most helpful results.[29,30]

The percentage weight loss is a relatively objective measure of dehydration. It does require accurate measurement on the same scale with the child undressed. The initial weight is subtracted from rehydration weight and taken as a percentage of the rehydration weight. For example, a rehydrated child weighing 10 kg who was 9 kg on admission would be 10% dehydrated. The two weights should be taken at the same time of day, but not more than 24 hours apart to exclude changes from loss of subcutaneous tissues due to the catabolic state.

Studies in Darwin have found a relatively low level of agreement between clinical assessment of dehydration and percentage weight loss (kappa agreement 0.30 and Pearson correlation 0.56). Clinical dehydration correlated better with a low bicarbonate and reflected how sick the child appeared. The percentage weight loss tended to underestimate the degree of dehydration because of ongoing losses from osmotic diarrhoea. It could potentially overestimate the degree of dehydration if the child were given excessive IV fluids and developed puffy eyes. Note that the degree of clinical dehydration may be underestimated in obese children and overestimated when children are wasted or septic. Urinary output and specific gravity are helpful to confirm that a child has been adequately rehydrated and is passing frequent urine of low specific gravity.

[Editor: At the time of presenting to a clinic with diarrhoea, many children will have a recent routine weight recorded in their notes. As long as this is a weight from a time when they were well, and is recent (a week

or so), then it can be used to estimate dehydration. This has been retained in the fourth edition protocol.]

Management

Rehydration

Oral rehydration with an appropriate solution is a highly effective means of rehydration, which uses the principle of glucose-facilitated sodium transport.[24,31] A NSW study found that oral rehydration was under-utilised in Australian children with diarrhoea.[32] Oral rehydration is time consuming for caregivers, particularly with vomiting. Vomiting usually resolves and can be managed with small, frequent amounts of oral rehydration solution (e.g. 5 mL every two minutes)[24], but this requires a compliant and motivated mother.

The optimal concentration of an oral rehydration solution is approximately 60 mmols/L of sodium, 20 mmol/L of potassium, 110 mmol/L (2.5%) of glucose and an osmolality of about 220.[33,34] Soft drinks, juices and similar solutions tend to be too hypertonic and low in electrolytes. Cereal-based oral rehydration solutions (e.g. rice) have not been shown to have a definite benefit in non-cholera diarrhoea compared to glucose-based oral rehydration solution[34], but there is anecdotal evidence that it may be more palatable. However, the most likely reason for a child refusing to drink oral rehydration solution because of the taste is because he/she is not actually dehydrated. Dehydrated children will not refuse to drink oral rehydration solution because of taste.

An important advance in rehydration has been the change to rapid rehydration over four hours, except for rare causes of severe hypernatraemia. This was introduced as best practice by WHO in the 1980s, but has only been adopted by developed countries in the last few years.[24,31] Rapid intravenous rehydration with Ringer's lactate (Hartmann's solution) is now best practice for moderate to severe dehydration, or when oral rehydration is inappropriate or fails. The only contra-indications to a trial of oral rehydration therapy are shock, coma, ileus and severe hypokalaemia. Rapid rehydration aims to correct the child's deficit over four hours. Thus, a 10 kg child who is 10% dehydrated would receive one litre of Ringer's lactate over four hours. Although no studies have specifically compared rapid rehydration to slower rehydration, a number of studies have found rapid rehydration to be successful.[35] There is no evidence of a benefit from the addition of bicarbonate to rehydration solutions[36–38], however this has never been tested in Aboriginal children. This is of interest because they tend to have extremely high rates of acidosis with acute gastroenteritis (raising the possibility of a role for bicarbonate). Note that oral rehydration contains 10 mmol/L of citrate as base and Ringer's lactate contains 40 mmol/L of lactate as base. No study has compared Ringer's lactate to 0.9% normal saline for rehydration, but most recommendations in paediatrics prefer Ringer's lactate for rehydration, although the Advanced Paediatric Life Support and ICU guidelines favour normal saline.[39] Note that alkalosis (e.g. pyloric stenosis) is a relative contraindication to the use of Ringer's lactate.

There is a continuing controversy about the use of colloid (e.g. albumin) versus crystalloid (e.g. Ringer's lactate) solutions for volume replacement in critically ill patients. A systematic review[40,41] did not support the use of colloids for volume replacement and this issue is now the subject of an Australian multicentre trial in adults. Colloids have

never been standard treatment for rehydration so are best avoided in diarrhoea.

Early feeding

The duration of diarrhoea can be reduced by 0.43 (0.12–0.74) days by early feeding of children with acute gastroenteritis, which also has added nutritional benefits.[42] The best foods to be introduced in the treatment of acute gastroenteritis are complex carbohydrates (e.g. rice, wheat, bread, and cereals) yoghurt, fruit and vegetables. Fatty foods or high sugar foods — such as tea, juices or soft drinks — should be avoided.[31]

Anti-diarrhoeals

The current evidence does not support the use of anti-diarrhoeal drugs, such as Loperamide, opiates, anti-cholinergic agents or bismuth subsalicylate. None of the guidelines recommends their use. The only generally accepted diarrhoeal indication for the use of antibiotics is dysentery, particularly the acute phase of Shigella infection or a Salmonella enteric infection with fever in the very young infant. Co-trimoxazole would be the oral drug of choice since there are concerns about resistance to amoxycillin, and norfloxacin is not approved for use in children.

There is specific and effective treatment for giardiasis with tinadazole or metronidazole, which is worth treating in cases of persistent diarrhoea. Only half of cases will be picked up on stool microscopy, so treatment without a stool result is acceptable in persistent diarrhoea (>10 days). Albendazole for three days is only a moderately effective treatment for Strongyloides, and needs to be repeated a week later. Follow-up with repeat stool examination is important in these children in view of the dangers of chronic strongyloidiasis (e.g. with steroid treatment). Albendazole is also effective for Trichuris and hookworm, although they are not causes of acute diarrhoea. Other than the above, there is no evidence of a benefit for treating watery diarrhoea with antibiotics, indeed, there is a distinct disadvantage in that it prolongs the carrier state for Salmonella and could induce haemolytic uraemic syndrome in a child carrying an enterohaemorrhagic E. coli.

Zinc and vitamin A

Zinc treatment reduces the duration and severity of acute and persistent diarrhoea.[43] Daily low dose zinc supplements also have an important preventive action against diarrhoea.[44] There is good evidence of a benefit of vitamin A in reducing mortality in measles[45], but the evidence in diarrhoeal disease is still conflicting, although it probably reduces episodes of persistent diarrhoea.[46] Large doses of vitamin A (e.g. 200 000 IU/3-monthly) and prolonged high dose zinc (10 mg/kg for three weeks) are potentially dangerous. There are interactions between micronutrients — such as zinc, iron and vitamin A — which are still unclear[47,48], but local dietary and infectious circumstances may change the effectiveness of micronutrient therapy in different settings.

A recent study of combined zinc and vitamin A synergistically reduced the prevalence of persistent diarrhoea and dysentery.[49] Although zinc was associated with a significant increase in acute lower respiratory infection, this adverse effect was reduced by the interaction between zinc and vitamin A. There are many studies under way examining this question so we need to await better evidence. In terms of folic acid for the treatment

of diarrhoea, an unpublished study by Jim Thurley at Alice Springs Hospital found some benefit for folic acid in diarrhoea, but two randomised controlled trials have found no benefit compared to placebo.[46,50]

[Editor: At the moment 'Liquid Zinc' is the only suitable formulation available but it has the problems of needing large volumes (15 ml) for small children, and poor taste. We hope to find a better alternative formulation in the future. This may need to be prepared by regional pharmacies. RDH pharmacy grinds up 50 mg tablets into a suspension, though the shelf life is only seven days in the refrigerator.]

New treatments

There are some interesting novel therapies for diarrhoea under investigation. Racecadotril is an inhibitor of enkephalins (endogenous opioid peptides) that causes decreased intestinal hypersecretion. A Peruvian study showed a decreased duration and severity of diarrhoea in children in the Racecadotril-treated group.[51] Gum arabic is a soluble polysaccharide fibre with proabsorptive properties which affects intestinal nitrous oxide (NO) and potassium channels, and may improve sodium absorption in diarrhoea.[52,53] Nitazoxanide is a new broad-spectrum antimicrobial agent which has been shown to be effective against giardiasis, amoebic dysentery and cryptosporidiosis.[54,55] Rifaximin is a non-absorbable antibiotic which is effective in the treatment of small bowel bacterial overgrowth.[56] Finally, probiotics — such as Lactobacillus GG (healthy germs) — have been shown to shorten the course of diarrhoeal disease, particularly in rotavirus infection.[57] This is currently the subject of a trial at Royal Darwin Hospital, since the benefits in Aboriginal children who are breastfed with bacterial diarrhoea are uncertain.

[Editor: The recommendation to change formula-fed babies with persisting diarrhoea to a lactose-free formula is based on the high prevalence of lactose intolerance seen in hospitalised babies with gastroenteritis. An alternative option would have been to recommend testing all formula-fed babies with persisting diarrhoea for reducing substances as evidence of lactose intolerance. We felt this was probably difficult to do in remote practice, and most such babies should be tried on a de-lact formula anyhow.

Testing urine M/C/S for possible UTI in children with persisting diarrhoea has been dropped from the fourth edition protocol. The rate of proven UTI with acute diarrhoea or FTT is 15–20% in hospital. The most practical and reliable test is a fresh bag urine for nitrites (dipstick). Sending a bag urine for culture is likely to be a waste of time, with a very high false positive rate.

The recommendation to collect a daily stool specimen for three days for M/C/S has been dropped because it is usually difficult to get stool specimens from Aboriginal patients, and because the additional yield from two more specimens is limited. Stool cultures miss over 35% of pathogens anyway by not checking E. coli probes. The treatment protocol includes treating for Giardia anyhow.]

References

1. Anonymous. Learning lessons: an independent review of Indigenous education in the Northern Territory. 1999. Darwin, NT Department of Education.

2. d'Espaignet ET, Kennedy K, Paterson BA & Measey MA. From infancy to young adulthood: health status in the Northern Territory. Darwin: Territory Health Services, Epidemiology Branch, 1998; 1–50.
3. Guthridge S, Cairnduff S, Gollow P, Pearce M & Kennedy K. Structure, Function and Health: a review of the health impact of infrastructure change in remote Aboriginal communities of the Top End. Darwin: THS/CRCATH, 2001.
4. Kukuruzovic R, Haase A, Dunn K, Bright A & Brewster DR. Intestinal permeability and diarrhoeal disease in Aboriginal Australians. Arch Dis Child 81:304–8 (1999).
5. Kukuruzovic R & Brewster DR. Small bowel intestinal permeability in Australian Aboriginal children. [unpublished manuscript].
6. Kukuruzovic RH & Brewster DR. Milk formulas in acute gastroenteritis and malnutrition: a randomised trial. [unpublished manuscript].
7. Kukuruzovic RH, Robins Browne RM, Anstey N & Brewster DR. Enteric pathogens, intestinal permeability and nitric oxide production in childhood diarrheal disease. [unpublished manuscript].
8. Newman RD, et al. A longitudinal study of Giardia lamblia infection in north-east Brazilian children. Trop Med Int Health 6:624–34 (2001).
9. Lunn PG, Erinoso HO, Northrop-Clewes CA & Boyce SA. Giardia intestinalis is unlikely to be a major cause of the poor growth of rural Gambian infants. J Nutr 129:872–7 (1999).
10. Fagundes-Neto U, Viaro T, Wehba J, Patricio FR & Machado NL. Tropical enteropathy (environmental enteropathy) in early childhood: a syndrome caused by contaminated environment. J Trop Pediatr 30:204–9 (1984).
11. Best JC, Welch JS, Filippich C & McPhee L. Treatment of intestinal parasites in Australian Aboriginal children. Med J Aust 1:14–20 (1976).
12. Gracey M, et al. Intestinal pathogens and parasites in Australian aboriginal children from birth to two years of age. Trans R Soc Trop Med Hyg 86:222–3 (1992).
13. Hopkins RM, et al. The prevalence of hookworm infection, iron deficiency and anaemia in an Aboriginal community in north-west Australia. Med J Aust 166:241–4 (1997).
14. Jones HI. Intestinal parasite infections in Western Australian Aborigines. Med J Aust 2:375–80 (1980).
15. Meloni BP, Thompson RC, Hopkins RM, Reynoldson JA & Gracey M. The prevalence of Giardia and other intestinal parasites in children, dogs and cats from aboriginal communities in the Kimberley. Med J Aust 158:157–9 (1993).
16. Kukuruzovic RH, Brewster DR, Gray E & Anstey NM. Increased nitric oxide production in acute diarrhoea is associated with abnormal gut permeability, hypokalaemia and malnutrition. [Unpublished manuscript].
17. Guerrant RL. et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 32:331–51 (2001).
18. Brunser O. et al. Chronic environmental enteropathy in a temperate climate. Hum Nutr Clin Nutr 41:251–61 (1987).
19. Lunn PG, Northrop Clewes CA & Downes RM. Intestinal permeability, mucosal injury, and growth faltering in Gambian infants. Lancet 338:907–10 (1991).
20. Northrop Clewes CA, Lunn PG & Downes RM. Lactose maldigestion in breast-feeding Gambian infants. J Pediatr Gastroenterol Nutr 24:257–63 (1997).
21. Gracey M, Williams P & Houston S. Environmental health conditions in remote and rural aboriginal communities in western Australia. Aust NZ J Public Health 21:511–18 (1997).
22. Ruben AR & Walker A. Malnutrition among rural Aboriginal children in the Top End of the Northern Territory. Med J Aust 162:400–3 (1995).
23. Skull SE, Ruben AR & Walker A. Malnutrition and microcephaly in Australian Aboriginal children. Med J Aust 166:412–14 (1997).
24. Armon K, Stephenson T, MacFaul R, Eccleston P & Werneke U. An evidence and consensus based guideline for acute diarrhoea management. Arch Dis Child 85:132–42 (2001).

25. Murphy MS. Guidelines for managing acute gastroenteritis based on a systematic review of published research. Arch Dis Child 79:279–84 (1998).
26. Mackenzie A, Barnes G & Shann F. Clinical signs of dehydration in children. Lancet 2:605–7 (1989).
27. Gorelick MH, Shaw KN & Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. Pediatrics 99:E6 (1997).
28. Gorelick MH, Shaw KN, Murphy, KO & Baker MD. Effect of fever on capillary refill time. Pediatr Emerg Care 13:305–7 (1997).
29. Vega RM & Avner JR. A prospective study of the usefulness of clinical and laboratory parameters for predicting percentage of dehydration in children. Pediatr Emerg Care 13:179–82 (1997).
30. Teach SJ, Yates EW & Feld LG. Laboratory predictors of fluid deficit in acutely dehydrated children. Clin Pediatr Phila 36:395–400 (1997).
31. Anonymous. Practice parameter: the management of acute gastroenteritis in young children. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Pediatrics 97:424–35 (1996).
32. Porteous JE, et al. Management of childhood gastroenteritis in the community. Med J Aust 167:195–8 (1997).
33. Anonymous & Anonymous. Multicentre evaluation of reduced-osmolarity oral rehydration salts solution. International Study Group on Reduced-osmolarity ORS solutions. Lancet 345:282–5 (1995).
34. Hahn S, Kim Y & Garner P. Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review. Br Med J 323:81–5 (2001).
35. Reid SR & Bonadio WA. Outpatient rapid intravenous rehydration to correct dehydration and resolve vomiting in children with acute gastroenteritis. Ann Emerg Med 28:318–23 (1996).
36. Elliott EJ, Armitstead JC, Farthing MJ & Walker SJ. Oral rehydration therapy without bicarbonate for prevention and treatment of dehydration: a double-blind controlled trial. Aliment Pharmacol Ther 2:253–62 (1988).
37. Elliott EJ, Walker SJ & Farthing MJ. The role of bicarbonate and base precursors in treatment of acute gastroenteritis. Arch Dis Child 62:91–5 (1987).
38. Rolston DD & Mathan VI. Effect of base precursors on water and electrolyte transport during oral hydration solution perfusion in secreting rat intestine. Dig Dis Sci 37:47–52 (1992).
39. Phillips B, Zideman D, Garcia-Castrillo L, Felix M & Shwarz-Schwierin V. European Resuscitation Council Guidelines 2000 for Advanced Paediatric Life Support. A statement from Paediatric Life Support Working Group and approved by the Executive Committee of the European Resuscitation Council. Resuscitation 48:231–4 (2001).
40. Alderson P, Schierhout G, Roberts I & Bunn F. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev CD000567 (2000).
41. Bunn F, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. The Albumin Reviewers. Cochrane Database Syst Rev CD001208 (2000).
42. Brown KH, et al. Effect of continued oral feeding on clinical and nutritional outcomes of acute diarrhea in children. J Pediatr 112:191–200 (1988).
43. Bhutta ZA, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am. J Clin Nutr 72:1516–22 (2000).
44. Bhutta ZA, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J Pediatr 135:689–97 (1999).
45. Glasziou PP & Mackerras DE. Vitamin A supplementation in infectious diseases: a meta-analysis. Br Med J 306:366–70 (1993).

46. Mahalanabis D & Bhan MK. Micronutrients as adjunct therapy of acute illness in children: impact on the episode outcome and policy implications of current findings. Br J Nutr 85 Suppl 2:S151–8, S151–S158 (2001).
47. Christian P & West KP Jr. Interactions between zinc and vitamin A: an update. Am J Clin Nutr 68:435S–441S (1998).
48. Munoz EC, Rosado JL, Lopez P, Furr HC & Allen LH. Iron and zinc supplementation improves indicators of vitamin A status of Mexican preschoolers. Am J Clin Nutr 71:789–94 (2000).
49. Rahman MM, et al. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. Br Med J 323:314–18 (2001).
50. Ashraf H, Rahman MM, Fuchs GJ & Mahalanabis D. Folic acid in the treatment of acute watery diarrhoea in children: a double-blind, randomized, controlled trial. Acta Paediatr 87:1113–15 (1998).
51. Salazar-Lindo E, Santisteban-Ponce , Chea-Woo E & Gutierrez M. Racecadotril in the treatment of acute watery diarrhea in children. N Engl J Med 343:463–7 (2000).
52. Rehman K, Wingertzahn MA, Harper RG & Wapnir RA. Proabsorptive action of gum arabic: regulation of nitric oxide metabolism in the basolateral potassium channel of the small intestine. J Pediatr Gastroenterol Nutr 32:529–33 (2001).
53. Wapnir RA, Teichberg S, Go JT, Wingertzahn MA & Harper RG. Oral rehydration solutions: enhanced sodium absorption with gum arabic. J Am Coll Nutr 15:377–82 (1996).
54. Rossignol JF, Ayoub A & Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. J Infect Dis 184:103–6 (2001).
55. Rossignol JF, Ayoub A & Ayers MS. Treatment of diarrhea caused by Giardia intestinalis and Entamoeba histolytica or E. dispar: a randomized, double-blind, placebo-controlled study of nitazoxanide. J Infect Dis 184:381–4 (2001).
56. Corazza GR, et al. Non-absorbable antibiotics and small bowel bacterial overgrowth. Ital J Gastroenterol 24:4–9 (1992).
57. Guandalini S, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr 30:54–60 (2000).