━ *Clinical Guideline* ━

Guidelines for the Management of Acute Diarrhoea in Young Children

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These guidelines are not intended for the management of acute diarrhoea in neonates.

Disclaimer

These guidelines have been developed by the Hong Kong College of Paediatricians and the authors, according to the state of medical knowledge at the time of compilation. These guidelines are for ***general guidance only*** and are designed ***to provide information to assist decision making***. Paediatricians should use their up-to-date medical knowledge, clinical data of the patients and their own clinical judgement in applying the recommendations in this document to the management of individual patients.

Explanatory Notes on Level of Evidence and Grading System on Recommendation

The definition of types of evidence and grading recommendations originate from the US Agency for Health Care Policy and Research (AHCPR) and are also recommended and used by the Royal College of Paediatrics and Child Health.

Levels of evidence

Level	Type of evidence (based on AHCPR 1992)
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of recommendations

Grade	Type of recommendation (based on AHCPR 1994)
A (Levels Ia, Ib)	Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (Level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Evidence is graded upon the methodological qualities. Guidelines normally contain many different recommendation based upon different levels of evidence. It is important that users are aware of the level of evidence on which each guideline recommendation is based. The link between guideline recommendation and the supporting evidence should be made explicit. Separating the strength of the recommendation from the level of evidence helps in situations where extrapolation is required to take the evidence of a methodologically strong study and apply it to the target population. Gradings of recommendation in addition to level of evidence allow more flexibility for future revision. Currently, there are discussions on taking account of relevant high quality non-RCTs and qualitative research and to incorporate them into appropriate grading system.

Key Recommendations

Assessment
- Signs for assessment of dehydration should be used collectively.

Signs and symptoms	No signs of dehydration	Mild to Moderate dehydration	Severe signs of dehydration
INITIAL ASSESSMENT			
General condition	*Well, alert*	*Restless, irritable, floppy*	*Lethargic or unconscious*
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mucous membrane	Moist	Dry	Very dry
Thirst	*Drinks normally, not thirsty*	*Thirsty, drinks eagerly*	*Drinks poorly or not able to drink*
Skin turgor (Pinch)	*Goes back quickly*	*Goes back slowly*	*Goes back very slowly >2s*
ADDITIONAL INDICATORS			
Extremities	Warm normal capillary refill	Delayed capillary refill	Cool, mottled, pale Capillary refill >2s
Respiration	Normal	Deep	Deep and rapid
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Blood pressure	Normal	Normal	Normal to reduced
Urine output	Normal	Reduced (<1 mL/kg/h)	None for many hours (<<1 mL/kg/h)
Fontanelle if open	Normal	Sunken	Sunken

- Children with diarrhoea who have signs of dehydration, signs of toxaemia, young age of less than 3 months, or blood in the stool should be considered for hospital admission.

Oral Rehydration Therapy
- Oral Rehydration Therapy (ORT) is the preferred treatment of mild to moderate dehydration in children with acute diarrhoea.
- Hypotonic ORS is preferred in developed countries.
- ORT should be under medical supervision and can usually be completed over four hours.
- ORT can successfully rehydrate most children even with vomiting.
- In hypernatraemic dehydration, ORT is safer than intravenous rehydration provided child is able to drink.

Nutrition Therapy
- Breastfeeding should continue through rehydration and maintenance phases of treatment.
- Dehydrated infants and children should be fed age-appropriate diets as soon as they are rehydrated.
- Gradual reintroduction of milk-based formulas or cow's milk is not routinely required.
- Lactose free or lactose-reduced formulas are not routinely required.

Drug Therapy
- Antibiotics are not recommended for uncomplicated diarrhoea.
- Probiotics (Lactobacillus) are safe and effective and can be recommended for the treatment of children with acute infectious diarrhoea.
- Antidiarrhoeal drugs are not routinely recommended for acute diarrhoea in children.

Recommendations for Management of Acute Diarrhoea in Young Children

Assessment
- Assessment determines treatment modality and monitors treatment response. (**Level IIa Evidence, Grade B Recommendation**)
- Reliable signs for assessment of dehydration include: (**Level IIa Evidence, Grade B Recommendation**)

Signs and symptoms	No signs of dehydration	Mild to moderate dehydration	Severe signs of dehydration
INITIAL ASSESSMENT			
General condition	*Well, alert*	*Restless, irritable, floppy*	*Lethargic or unconscious*
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mucous membrane	Moist	Dry (inaccurate in mouth breather)	Very dry
Thirst	*Drinks normally, not thirsty*	*Thirsty, drinks eagerly*	*Drinks poorly or not able to drink*
Skin turgor (Pinch)	*Goes back quickly*	*Goes back slowly*	*Goes back very slowly >2 s*
ADDITIONAL INDICATORS			
Extremities	Warm normal capillary refill	Delayed capillary refill	Cool, mottled, pale Capillary refill >2 s
Respiration	Normal	Deep	Deep and rapid
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Pulse volume	Normal	Normal or slightly decreased	Moderately decreased
Blood pressure	Normal	Normal	Normal to reduced
Urine output	Normal	Reduced (<1 mL/kg/h)	None for many hours (<<1 mL/kg/h)
Fontanelle if open	Normal	Sunken	Sunken

- Conventional clinical signs of dehydration are valid and reliable when used collectively, but individually lack sensitivity and specificity. (**Level IIa Evidence, Grade B Recommendation**)
- Children with diarrhoea who have signs of dehydration, signs of toxaemia, young age of less than 3 months, or blood in the stool should be considered for hospital admission. (**Level IV Evidence, Grade C Recommendation**)

Investigation
- Plasma or serum biochemistry tests are indicated for patients with severe dehydration and probably also for those patients with some signs of dehydration who require intravenous fluid replacement. (**Level IV Evidence, Grade C Recommendation**)

- Stool culture should be considered for patients who have blood in the diarrhoeal stool, persistent fever or signs of toxicity. (**Level IV Evidence, Grade C Recommendation**)
- Stool for rotavirus antigen testing is not routinely required as it should not alter management. However it is useful for diagnostic purposes. (**Level IV Evidence, Grade C Recommendation**)

Oral Rehydration Therapy
- Oral Rehydration Therapy (ORT) is the preferred treatment of mild to moderate dehydration in children with acute diarrhoea. (**Level Ia Evidence, Grade A Recommendation**) Children who are very ill, lethargic, drink poorly, with shock or near shock should be treated initially with IV solutions, details of which are not

discussed in this guideline. When the child's condition has stabilised and mental status is satisfactory, ORT may be instituted. **(Level IV Evidence, Grade C Recommendation)** ORT should not be given to children with intestinal ileus until bowel sounds are audible, **(Level IV Evidence, Grade C Recommendation)** or in the presence of glucose malabsorption i.e. patients with dramatic increase in stool output with ORT and glucose or reducing substances in the stool. **(Level IV Evidence, Grade C Recommendation)**

- Standard WHO-ORS, hypotonic ORS and rice-based ORS are all effective for the treatment of dehydration. **(Level Ia Evidence, Grade A Recommendation)** However hypotonic ORS with reduced sodium (50-75 mmol/L) and glucose (75-111 mmol/L) concentration and low osmolarity (200-250 mmol/L) is preferred in developed countries where mainly non-cholera diarrhoea occurs. **(Level IV Evidence, Grade C Recommendation)** Compared to WHO-ORS, hypotonic ORS may decrease stool output and shorten duration of diarrhoea, without increased risk of hyponatraemia. **(Level Ia Evidence, Grade A Recommendation)** Rice-based ORS does not have beneficial effects over the WHO-ORS in the treatment of dehydration due to non-cholera diarrhoea, especially when food is given immediately after rehydration. **(Level Ia Evidence, Grade A Recommendation)**

- Oral rehydration can usually be completed over four hours. **(Level IV Evidence, Grade C Recommendation)**
    - NO signs of dehydration
        give maintenance therapy
    - Mild-moderate dehydration
        give 50-75 ml/kg ORS

Rehydration should be carried out under medical supervision and regular and frequent assessment of hydration status is essential. **(Level IV Evidence, Grade C Recommendation)** ORT may fail in children with continuing rapid stool loss (>10-20 ml/kg/hour), insufficient intake of ORS or frequent, severe vomiting. **(Level IV Evidence, Grade C Recommendation)** If the child still has signs of dehydration at the end of four hours, appropriate rehydration therapy should be instituted accordingly.

- Maintenance fluids can be given as breast milk, formula, or other fluids appropriate for age, offered *ad libitum*. **(Level IV Evidence, Grade C Recommendation)** More fluids than usual should be offered to prevent dehydration. **(Level IV Evidence, Grade C Recommendation)** Drinks sweetened with sugar (e.g. soft drinks, sweetened juices) should be avoided as they may cause osmotic diarrhoea and hypernatraemia. **(Level IV Evidence, Grade C Recommendation)**

- Ongoing losses can be replaced by normal diets given *ad libitum* in children with mild diarrhoea and NO signs of dehydration. **(Level IV Evidence, Grade C Recommendation)** In high risk cases with persistent profuse diarrhoea or vomiting, ongoing losses should be replaced with extra feeds of low-sodium ORS (40-60 mmol/L of sodium). **(Level IV Evidence, Grade C Recommendation)** When high-sodium ORS (>60 mmol/L) is used to replace ongoing losses after rehydration, other low-sodium fluids (e.g. breast milk, formula, or water) should be given in alternate feeds. **(Level IV Evidence, Grade C Recommendation)** The following guide may be useful for caregivers to replace ongoing losses (stool and vomitus) during both rehydration and maintenance therapy: **(Level IV Evidence, Grade C Recommendation)**

    Each watery or loose stool:
<2 years of age:	50-100 ml
	(¼ to ½ a large cup)
2-10 years:	100-200 ml
	(½ to 1 large cup)
OR	10 ml/kg

    Each episode of emesis: 2 ml/kg

- Families should be advised to seek further medical advice should the child: **(Level IV Evidence, Grade C Recommendation)**
    - Starts to pass many watery stools
    - Has repeated vomiting
    - Becomes very thirsty
    - Is eating or drinking poorly
    - Develops a fever
    - Has blood in the stool
    - Deteriorates in any other way

- ORT can successfully rehydrate most children even with vomiting. **(Level Ia Evidence, Grade A Recommendation)** Small volumes of ORS (5-10 ml) should be administered every 1-2 minutes, with a gradual increase in the amount consumed. **(Level IV Evidence, Grade C Recommendation)** Continuous, slow infusion of ORS via a nasogastric tube may be an alternative in non-comatose patients and those without ileus. **(Level III Evidence, Grade B Recommendation)**

- In hypernatraemic dehydration ORT is safer than intravenous rehydration. **(Level Ib Evidence, Grade A Recommendation)** Provided the child's neurological

status is stable and the child is able to drink, use "Slow ORT", aiming to complete rehydration over 12 hours and monitoring serum sodium to avoid a rapid reduction. **(Level III Evidence, Grade B Recommendation)**

Nutrition Therapy

- Breastfeeding should continue through rehydration and maintenance phases of treatment. **(Level Ib Evidence, Grade A Recommendation)**
- Exclusive breastfeeding should be promoted to reduce the severity of acute diarrhoea in infants during the first six months of life. **(Level IIa Evidence, Grade B Recommendation)**
- Children who are not dehydrated should continue to be fed age-appropriate diets. **(Level Ia Evidence, Grade A Recommendation)**
- Dehydrated infants and children should be fed age-appropriate diets as soon as they are rehydrated (usually within 4 hours). **(Level Ia Evidence, Grade A Recommendation)**
- Gradual reintroduction of milk-based formulas or cow's milk is not routinely required. **(Level Ia Evidence, Grade A Recommendation)**
- Lactose free or lactose-reduced formulas are not routinely required. **(Level Ia Evidence, Grade A Recommendation)** These formulas may be considered if there is no improvement in the stool consistency after several days or if reducing substances are identified in the stool. **(Level IV Evidence, Grade C Recommendation)**
- Complex carbohydrates (e.g. rice, wheat, potatoes, bread and cereals), lean meat, yoghurt, fruits, and vegetables are better tolerated and more preferred than foods which are sugary (e.g. tea, juices and soft drinks) or fatty. **(Level IV Evidence, Grade C Recommendation)**

Drug Therapy

Antibiotics

- Antibiotics are not recommended for uncomplicated diarrhoea. **(Level III Evidence, Grade B Recommendation)**
- Most cases of *Salmonella* gastroenteritis do not require antibiotic therapy as symptoms are not improved by antibiotics **(Level Ib Evidence, Grade A Recommendation)**

- Parenteral antibiotics, e.g. third generation cephalosporins may be required for young infants (<3 months), any ill or septic looking patient and immunocompromised children with *Salmonella gastroenteritis* who have a higher risk of complications. **(Level IV Evidence, Grade C Recommendation)**
- *Campylobacter* gastroenteritis is usually self-limiting and antibiotic may only be of value if given early. Antibiotic may be indicated for children in institutional settings to shorten bacterial excretion. **(Level IV Evidence, Grade C Recommendation)**
- Shigellosis is highly infectious and notifiable. Antibiotic may shorten the infectious period but the disease is often self-limiting and hence antibiotic is used in ill patients or those who are still symptomatic when the pathogen is detected. **(Level IV Evidence, Grade C Recommendation)**
- Antibiotics are not usually required for diarrhoeagenic *E. Coli, Yersinia enterocolitica, Vibrio parahaemolyticus, Aeromonas spp., Plesiomonas spp*. Oral metronidazole or vancomycin is indicated for severe *Clostridium difficile* associated diarrhoea. Metronidazole is helpful for *giardia lamblia*. **(Level IV Evidence, Grade C Recommendation)**

Probiotics

- Probiotics (Lactobacillus) are safe and effective and can be recommended for the treatment of children with acute infectious diarrhoea. **(Level Ia Evidence, Grade A Recommendation)**

Antidiarrhoeal agents

- Antidiarrhoeal agents are not routinely recommended for acute diarrhoea in children. **(Level IV Evidence, Grade C Recommendation)**
- These agents should not be used in children with fever, toxaemia or blood in the stool. **(Level IV Evidence, Grade C Recommendation)**
- Users of these agents as adjunctive therapy should pay attention to precautions and possible risks. Attention to the appropriate dosage and proper education of parents are prudent. **(Level IV Evidence, Grade C Recommendation)**

Background

Acute diarrhoea is a very significant cause of morbidity amongst hospitalised children in Hong Kong. Less data is available for ambulatory children. Approximately 12% of all paediatric medical admissions to Hospital Authority Hospitals for the two-year period July 1997 to June 1999 were due to acute diarrhoea (Table 1). Approximately 10% of these admissions were due to rotavirus and 11% to *Salmonella*. However these percentages are believed to underestimate the true burden of these pathogens.[1] A prospective study over a one year period at one hospital in Hong Kong showed that approximately one third of diarrhoeal admissions were due to rotavirus, one third to bacteria (majority *Salmonella*) and the remaining one third had no specific organism identified.[2] Pathogenic *E. Coli* were not a common cause of acute diarrhoea in this population.[2] Shigella was uncommon and tended to cause disease in older children, whereas *Salmonella* mainly affected the younger infants. The economic importance of rotavirus infection in Hong Kong has been highlighted, although the impact of other causes of viral diarrhoea are less well quantified.[1,3] A number of Hong Kong studies have looked at rotavirus gastroenteritis in hospital and community settings (Table 2). In community settings rotavirus is responsible for a smaller proportion of children assessed with diarrhoea.

Table 1   Diarrhoea-associated hospitalisations by reported diagnosis among 106,919 children aged 1-59 months, Hong Kong Hospital Authority Hospitals from 1 July 1997 to 30 June 1999

	ICD codes	Primary diagnosis[†] n (%)
Presumed infectious	009.0-009.3	5753 (46.7)
Presumed non-infectious	558.9, 787.91	3358 (27.3)
Viral[*]	008.6-008.8	183 (1.5)
Rotavirus	008.61	1270 (10.3)
Cholera	001-001.9	1 (0)
Salmonella	002-003.9	1347 (10.9)
Shigella	004-004.9	66 (0.5)
Food poisoning	005-005.9	38 (0.3)
E. Coli & others	008-008.5	241 (2.0)
Total diarrhoea		12257 (12.2%)
All other diseases		94662 (87.8%)

([*]Excludes rotavirus; [†]Primary diagnosis code only)

Table 2   Review of previous Hong Kong studies assessing rotavirus disease burden

	Year	Duration (mo)	n	% rotavirus
Active surveillance studies				
Prince of Wales Hospital[2]	94-95	12	388	35
Queen Mary Hospital[4]	82-85	30	2228	30
Queen Mary Hospital[5]	83-85	30	2246	24
Queen Mary Hospital[6]	83-84	12	899	28.5
Passive surveillance and laboratory data				
Prince of Wales Hospital[1]	87-96	120	7945	28[*]
Community and laboratory studies				
Kwun Tong Community[7]	84-86	36	637	11[†]
Prince of Wales Hospital[8]	84-90	80	3267	34[‡]
Government Virus Laboratory[3]	87-92	72	27618	14[§]

[*]2213 laboratory reports were positive for rotavirus in children under five years during a period when 7,945 children of this age were admitted with a diagnosis of diarrhoea. However only 14% of the diarrhoea admissions were classified as viral diarrhoea indicating under-reporting in the patient discharge diagnosis; [†]Community study; [‡]Laboratory based study of positive isolates; [§]16.7% of stools specimens were positive for viruses and 84.4% of viral isolates were rotavirus (all ages).

Evidence for Recommendations

Assessment

Recommendation:

- Assessment determines treatment modality and monitors treatment response. **(Level IIa Evidence, Grade B Recommendation)**
- Reliable signs for assessment of dehydration include: **(Level IIa Evidence, Grade B Recommendation)**

Signs and symptoms	No signs of dehydration	Mild to moderate dehydration	Severe signs of dehydration
INITIAL ASSESSMENT			
General condition	***Well, alert***	***Restless, irritable, floppy***	***Lethargic or unconscious***
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mucous membrane	Moist	Dry (inaccurate in mouth breather)	Very dry
Thirst	***Drinks normally, not thirsty***	***Thirsty, drinks eagerly***	***Drinks poorly or not able to drink***
Skin turgor (Pinch)	***Goes back quickly***	***Goes back slowly***	***Goes back very slowly >2 s***
ADDITIONAL INDICATORS			
Extremities	Warm normal capillary refill	Delayed capillary refill	Cool, mottled, pale Capillary refill >2 s
Respiration	Normal	Deep	Deep and rapid
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Pulse volume	Normal	Normal or slightly decreased	Moderately decreased
Blood pressure	Normal	Normal	Normal to reduced
Urine output	Normal	Reduced (<1 mL/kg/h)	None for many hours (<<1 mL/kg/h)
Fontanelle if open	Normal	Sunken	Sunken

- Conventional clinical signs of dehydration are valid and reliable when used collectively, but individually lack sensitivity and specificity. **(Level IIa Evidence, Grade B Recommendation)**
- Children with diarrhoea who have signs of dehydration, signs of toxaemia, young age of <3 months, or blood in the stool should be considered for hospital admission. **(Level IV Evidence, Grade C Recommendation)**

Evidence:

A number of guidelines for the clinical assessment of dehydration have been proposed (Tables 3a-3d). The gold standard for diagnosis of dehydration is measurement of acute weight loss. However as the patient's true pre-illness weight is rarely known in the acute care setting, an estimate of the fluid deficit is mainly based on clinical assessment.

Assessment of dehydration is used to determine the treatment modality and to monitor the response to treatment.[9] **(Level IIa Evidence, Grade B Recommendation)** Weight after rehydration was found to be similar to pre-illness weight and the clinical signs used to assess dehydration were correlated with the actual dehydration.[9] **(Level IIa Evidence, Grade B Recommendation)** 3-4% is the level at which dehydration becomes clinically apparent, rather than 5% as is normally stated. Decreased peripheral perfusion, deep acidotic breathing and decreased skin turgor were found to be reliable signs,[10] together with circulatory collapse and capillary refill time ≥2 seconds showing severe dehydration ≥9%.[11] **(Level IIa Evidence, Grade B Recommendation)** Although actual weight losses of <3%, 3-8% and ≥9% better reflects the clinical findings of no signs of dehydration,

Table 3a   Clinical assessment of severity of dehydration (WHO) (http://www.who.int/chd/publications/cdd/textrev4.htm)

Signs and symptoms	None or mild	Moderate	Severe
Condition	Well, alert	Restless, irritable, floppy	Lethargic or unconscious
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mouth and tongue	Moist	Dry	Very dry
Thirst	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly or not able to drink
Skin turgor (Pinch)	Goes back quickly	Goes back slowly	Goes back very slowly >2 s

Table 3b   Clinical assessment of severity of dehydration[12,13]

No dehydration	Mild-moderate dehydration	Severe dehydration
<3% weight loss	3-8% weight loss	≥9% weight loss
NO SIGNS	• Dry mucous membrane (inaccurate in mouth breather) • Sunken eyes (and minimal or no tears) • Diminished skin turgor (pinch test >1 sec.) • Altered neurological state (drowsiness, irritability) • Deep (acidotic) breathing	Signs from the mild-moderate group PLUS • Decreased peripheral circulation (cool/mottled/pale peripheries; capillary refill time >2 sec.) • Circulatory collapse

Table 3c   Clinical assessment of severity of dehydration[9]

Signs and symptoms	None or mild	Moderate	Severe
General Condition			
Infants	Thirsty, alert, restless	Lethargic or drowsy	Limp, cold cyanotic extremities, maybe comatose
Older children		Alert, postural dizziness	Apprehensive, cold cyanotic extremities, muscle cramps
Radial pulse	Normal	Thready or weak	Feeble or impalpable
Respiration	Normal	Deep	Deep and rapid
Skin turgor (Pinch)	Retracts immediately	Retracts slowly	Retracts very slowly >2 s
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mucous membrane	Moist	Dry	Very dry
Urine output	Normal	Reduced	None for many hours

Table 3d   Clinical assessment of severity of dehydration (AAP)[14]

Signs and symptoms	Mild (3-5%)	Moderate (6-9%)	Severe (≥10%)
Blood pressure	Normal	Normal	Normal to reduced
Pulse volume	Normal	Normal or slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Skin turgor (Pinch)	Normal	Decreased	Decreased
Fontanelle	Normal	Sunken	Sunken
Mucous membrane	Slightly dry	Dry	Dry
Eyes	Normal	Sunken orbits	Deeply sunken orbits
Extremities	Warm normal capillary refill	Delayed capillary refill	Cool mottled
Mental status	Normal	Normal to listless	Normal to lethargic or comatose
Urine output	Slightly decreased	<1 mL/kg/h	<<1 mL/kg/h
Thirst	Slightly increased	Moderately increased	Very thirsty or too lethargic to indicate

mild to moderate dehydration and severe dehydration respectively, the weight loss classification of <5%, 5-10% and >10% is still widely used in clinical practice.

Conventionally used clinical signs of dehydration are valid and reliable when used collectively. However, when used individually parameters lack sensitivity and specificity (Table 4). **(Level IIb Evidence, Grade B Recommendation)**

The sensitivity of individual conventional clinical signs of dehydration ranged from 0.35 to 0.85. The specificity of these signs ranged from 0.53 to 0.97.[9]

Suggestions for Admission

Delphi consensus agreement was used to determine the recommendations for admission of children who present to hospital with diarrhoea in the United Kingdom.[13] Factors considered included level of hydration, presence of risk factors and assessment of the caregiver. However the extent to which these recommendations can be applied to children managed in community settings is less clear.

Investigations

Recommendation:
- Plasma or serum biochemistry tests are indicated for patients with severe dehydration and probably also for those patients with some signs of dehydration who require intravenous fluid replacement. **(Level IV Evidence, Grade C Recommendation)**
- Stool culture should be considered for patients who have blood in the diarrhoeal stool, persistent fever or signs of toxicity. **(Level IV Evidence, Grade C Recommendation)**
- Stool for rotavirus antigen testing is not routinely required, as it should not alter management. However

it is useful for diagnostic purposes. **(Level IV Evidence, Grade C Recommendation)**

Evidence:

There is limited evidence for cost-effectiveness of investigations in acute diarrhoea, especially for the local setting. Recommendations are based on consensus. The following investigations may be useful in patients with acute diarrhoea:
- Plasma/serum biochemistry (e.g. Na, K, HCO_3, urea, pH)
- Full blood counts
- Blood culture
- Stool bacterial culture
- Stool lactoferrin, occult blood and leucocytes
- Stool viral antigens, viral EM, viral culture
- Stool parasites
- Stool biochemistry for carbohydrate intolerance (pH, reducing substance and osmotic gap)

The value of plasma/serum electrolytes and urea level is obvious in the situation of severe dehydration. For lesser degrees of dehydration, the need for investigations is less clear cut and should be individualised. It has been suggested that electrolyte, urea/creatinine and bicarbonate levels should be checked in moderately dehydrated children whose histories or physical findings (e.g. "doughy" feel to skin) are inconsistent with straight-forward diarrhoeal episodes and in all severely dehydrated children.[13,14]

The band neutrophil counts, if raised, may help identify patient with bacterial gastroenteritis.[15] Blood culture is needed whenever patient appears toxic or ill. It is useful when managing cases of *Salmonella* gastroenteritis because

Table 4   Diagnostic performance of 10 individual clinical findings

	Sensitivity	Specificity
Decreased skin elasticity	0.35	0.97
Capillary refill >2 seconds	0.48	0.96
General appearance (ill-appearing, irritable, apathetic)	0.59	0.91
Absent tears	0.67	0.89
Abnormal respiration	0.43	0.86
Dry mucous membrane	0.80	0.78
Sunken eyes	0.60	0.84
Abnormal radial pulse	0.43	0.86
Tachycardia (heart rate >150)	0.46	0.79
Decreased urine output	0.85	0.53

of its propensity for deep invasion, especially for infants <3 months and in immuno-compromised patients.[16]

As stool bacterial yield on culture is low, especially in developed countries, a more selective approach to stool culture is recommended.[17] In one recent study in U.S.A., for example, only 7 out of 250 (2.8%) stools in paediatric patients admitted to hospital for diarrhoea were positive on culture.[15] Local experience suggests that the proportion of positive stool cultures may be up to 30% in hospitalised patients.[2] If stool culture is needed in a patient, one specimen suffices. In a local study, the first specimens already picked up the bacterial pathogen in 95% of cases.[18] A recent guideline suggested that stool be sent for microscopy, culture, sensitivity, and virology when there is a history suggestive of food poisoning, recent travel abroad or blood in the stool, with or without mucus. A stool should also be sent if the child is systemically unwell, or has severe or prolonged diarrhoea.[13]

Screening tests, including stool lactoferrin, occult blood and leucocytes, were studied for usefulness in assisting selective stool culture when these tests are positive. In terms of sensitivity with the least false positivity, stool lactoferrin is the best, followed by stool occult blood and finally stool leucocytes.[19] However, stool lactoferrin is not currently available locally. As the positive or negative predictive values would depend on the local prevalence of various bacterial pathogens, the result of overseas studies may not be directly applicable locally. Therefore the usefulness of these test on top of clinical judgement is unclear.

Retrospective analysis showed that viruses (rotavirus, adenovirus, astrovirus, Norwalk-like virus and calicivirus taken together) were present only in <20% of stools from infants and children less than five during the period from 1987 to 1992.[3] However, a more recent study suggests that approximately one third of children hospitalised with acute diarrhoea will have rotavirus.[2] Cost and epidemiological considerations will determine whether stool specimens should be tested for viruses.

Stool parasites are uncommonly detected in Hong Kong children with diarrhoea.[2] This is generally the case in developed countries where general hygienic standards are good.[17] Giardiasis should be considered when the child passes loose offensive frothy stools and in such situations fresh stools should be sent for immediate examination. Examining stools for parasites may be considered for children arriving from regions where the prevalence of infection is higher. As special detection method may be needed for some parasites, e.g. cryptosporidium, adequate communication with the laboratory is prudent when parasites are considered.

Oral Rehydration Therapy

Safety and Efficacy of Oral Rehydration Therapy

Recommendation

- Oral Rehydration Therapy (ORT) is the preferred treatment of mild to moderate dehydration in children with acute diarrhoea. **(Level Ia Evidence, Grade A Recommendation)** Children who are very ill, lethargic, drink poorly, with shock or near shock should be treated initially with IV solutions. When the child's condition has stabilised and mental status is satisfactory, ORT may be instituted. **(Level IV Evidence, Grade C Recommendation)** ORT should not be given to children with intestinal ileus until bowel sounds are audible, **(Level IV Evidence, Grade C Recommendation)** or in the presence of glucose malabsorption i.e. patients with dramatic increase in stool output with ORT and glucose or reducing substances in the stool. **(Level IV Evidence, Grade C Recommendation)**

Evidence

Replacement of fluid and electrolyte losses is the critical central element of effective treatment of acute diarrhoea. The discovery of coupled co-transport of sodium and glucose provides the scientific basis for ORT as an alternative to intravenous (IV) therapy. This co-transport mechanism works in an approximately equimolar ratio and remains intact even during copious secretory diarrhoea.[20]

In 1975, the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) agreed to promote a single solution (WHO-ORS) containing (in mmol/L): sodium 90, potassium 20, chloride 80, base 30 and glucose 111 (2%). Recently, the bicarbonate component of the WHO-ORS has been replaced with citrate because of its longer shelf-life. The standard WHO oral rehydration solution (ORS) can successfully rehydrate more than 90% of children with dehydration due to acute diarrhoea.[21] However, ORT does not reduce the rate of stool loss or the duration of diarrhoea, which are the main concerns of parents.[22]

In randomised controlled trials in which ORT was compared with standard intravenous therapy, both in developed[23-25] and developing[26] countries, ORT was as effective as IV therapy in rehydrating children. In addition

ORT was found to be more rapid in correcting dehydration and acidosis,[24] while being safer and with none of the complications associated with intravenous therapy.[23,26]

In a meta-analysis of the efficacy of glucose-based ORT in developed countries among well-nourished young children with acute diarrhoea, 6 randomised-control trials comparing ORT with intravenous rehydration treatment and 7 randomised-control trials comparing ORSs with different sodium contents were included.[21] The overall failure rate was 3.6% (95% CI, 1.4-5.8%) while the failure rate for those with or without IV arms were 5.7% (95% CI, 1.8-9.6%) and 3.0% (95% CI, 0.6-5.4%) respectively. Failure rates broken down by sodium content of the ORS failed to show a statistically significant difference. Iatrogenic hypernatraemia or hyponatraemia was only reported in 2 studies – hyponatraemia in 10 cases and hypernatraemia in 3 cases. When sodium content of ORS was divided into high (90 mmol/L), medium (50-75 mmol/L) and low (26-45 mmol/L), the number of cases of iatrogenic hyponatraemia was 1, 9 and 6 from the respective groups. One case of iatrogenic hypernatraemia occurred in each of the group. Therefore children rehydrated with medium to low sodium solutions may be at a slightly higher risk of mild iatrogenic hyponatraemia. When other outcome parameters including duration of diarrhoea, length of hospitalisation and weight gain at discharge were considered, there was a tendency favouring ORT over IV rehydration. There was little difference among these outcomes of ORSs with different concentration of sodium.

Composition of ORS

Recommendation
- Standard WHO-ORS, hypotonic ORS and rice-based ORS are all effective for the treatment of dehydration. **(Level Ia Evidence, Grade A Recommendation)** However hypotonic ORS with reduced sodium (50-75 mmol/L) and glucose (75-111 mmol/L) concentration and low osmolarity (200 -250 mmol/L) is preferred in developed countries where mainly non-cholera diarrhoea occurs. **(Level IV Evidence, Grade C Recommendation)** Compared to WHO-ORS, hypotonic ORS may decrease stool output and shorten duration of diarrhoea, without increased risk of hyponatraemia. **(Level Ia Evidence, Grade A Recommendation)** Rice-based ORS does not have beneficial effects over the WHO-ORS in the treatment of dehydration due to non-cholera diarrhoea, especially when food is given immediately after rehydration. **(Level Ia Evidence, Grade A Recommendation)**

Evidence
Despite the proven efficacy and safety of the WHO-ORS, there is concern over the risk of hypernatraemia in developed countries where children are well-nourished and mostly suffering from non-cholera diarrhoea with lower sodium loss in stool, especially in infants less than 3 months of age.[27] WHO actually recommended the use of complete WHO-ORS for initial rehydration only. During maintenance therapy, the addition of free water to the WHO-ORS in a ratio of 1:2 was recommended to give a sodium concentration of 60 mmol/L.[28]

Currently, WHO recommends using solutions with a glucose-to-sodium ratio of less than 1.4:1,[29] whereas the American Academy of Pediatrics recommends a ratio of less than 2:1.[30] 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 addition, perfusion studies in animals and humans have also shown that osmolarity rather than sodium concentration and the sodium-glucose ratio, may be the most critical determinant of intestinal absorption of an ORS solution.[31,32] From these studies, it was concluded that optimal water absorption could be obtained by using a hypotonic solution with a sodium concentration of 50-60 mmol/L and a glucose concentration of 50-100 mmol/L. In randomised controlled trials, oral rehydration solutions containing 50-60 mmol/L sodium are safe and effective treatment for the dehydration and electrolyte abnormalities associated with acute diarrhoea of varied aetiology and in all age groups including neonates, eliminating the need for additional free water for maintenance therapy.[23,27] Mild and asymptomatic hyponatraemia was observed in some children. In 1992, the European Society of Paediatric Gastroenterology and Nutrition (ESPGN) recommended an ORS solution containing 60 mmol/L sodium, 74-111 mmol/L glucose and an osmolarity between 200-250 mmol/L for European children (Table 5).[33] Very similar recommendations were made for United Kingdom children.[13]

In a few clinical trials comparing low sodium ORSs with WHO-ORS, stool output, fluid intake and treatment failures were reduced in children treated with hypotonic ORS without an increased risk of hyponatraemia (Tables of Evidence – Table C2). Studies that compared other high osmolarity ORSs with low osmolarity ORSs are shown in Tables of Evidence – Table C3.

In a multicentre evaluation of reduced-osmolarity ORS in developing countries, standard ORS with osmolarity of 311 mmol/L was compared to reduced-osmolarity ORS of 224 mmol/L (sodium 60 mmol/L, glucose 84 mmol/L) in the rehydration of mild to moderate dehydration in non-cholera diarrhoea.[34] Treatment with reduced-osmolarity ORS resulted in decreased stool output (39%), decreased ORS intake (18%), decreased duration of diarrhoea (22%) and increased urine output. The risk of developing or worsening hyponatraemia was not increased in children given the reduced-osmolarity ORS. A significant reduction in the need for unscheduled intravenous therapy of up to 33% was demonstrated in another recent multicentre, randomised, double-blind study in 5 countries including Bangladesh, Brazil, India, Peru and Vietnam. In this study, a reduced-osmolarity ORS (75 mmol/L sodium, 20 mmol/L potassium, 65 mmol/L chloride, 10 mmol/L citrate, 75 mmol/L glucose and osmolarity 245 mosmol/L) was compared with the standard WHO-ORS in 675 children. However, there was no significant difference in terms of stool output, duration of diarrhoea and percentage with vomiting. The risk of hyponatraemia at 24 hours was not significantly different but can be up to doubling the number when compared with the WHO group.[35]

In a recent systemic review of the effect of reduced osmolarity ORS in children, the results in 15 randomised controlled studies including 2397 children were analysed. Standard WHO-ORS was compared with reduced-osmolarity ORS (osmolarity <270 mosmol/L). Reduced-osmolarity ORS was associated with a 35% reduction in unscheduled intravenous therapy, a 20% reduction in stool output and a 30% reduction in vomiting, with no difference in the incidence of hyponatraemia.[36] Very similar results were shown in the systemic review of the Cochrane Library of reduced osmolarity ORS for treating dehydration caused by acute diarrhoea in children.[37] Based on this evidence, WHO has recently announced the use of a new formula for ORS with sodium 75 mmol/L, glucose 75 mmol/L and total osmolarity of 245 mosmol/L on 8 May 2002.[38]

The substitution of cereal for glucose in ORS is one of the many efforts to improve the WHO-ORS. The apparent superiority of rice-based ORS has been attributed to its capacity to release more glucose from rice starch than is present in glucose-based ORS, facilitating greater coupled transport with sodium while maintaining low osmolarity.[39] In addition to glucose polymers, cereal also provides amino acids and short chain peptides that have all been demonstrated to enhance sodium and water reabsorption without incurring an osmotic penalty in the gut.[40] Many

clinical trials have been conducted with conflicting results.[41] Most studies were characterised by highly heterogeneous patient groupings with different causes of diarrhoea. In addition, the quantity and quality of the maintenance diet often were not standardised, measured, or described adequately. Since early feeding reduces the severity, duration and nutritional consequences of diarrhoea, variations in diet may account for the differences in results.[42] Details of randomised controlled trials comparing rice-based ORS with WHO-ORS were shown in Tables of Evidence – Table C4. In a meta-analysis of 13 randomised clinical trials involving more than 1300 children and adults, the efficacy of rice-based ORS (containing 50-80 g/L rice powder) was compared with that of WHO-ORS. Rice-based ORS resulted in a significant reduction in stool output in the first 24 hours and reduction of duration of diarrhoea in adults and children with cholera, but not in children with non-cholera diarrhoea.[22] The authors concluded that "the benefit of rice-based ORS for children with acute, non-cholera diarrhoea should be more precisely defined before its practical value can be judged". In order to define more precisely the benefit of rice-based ORS for children with non-cholera diarrhoea, the meta-analysis was updated in 1996 by the addition of 9 trials in children with non-cholera diarrhoea. Rice-based ORS only caused a small and non-significant reduction in stool output.[43] The authors concluded that "rice-based ORS does not reduce stool output when compared with standard ORS in children with acute, non-cholera diarrhoea, especially when food is given immediately after rehydration". Similar results and conclusions were obtained in the systematic review of the Cochrane Library to assess the effects of rice-based ORS compared with WHO-ORS on reduction of stool output and duration of diarrhoea.[44]

Rehydration Regimen

Recommendation
- Oral rehydration should usually be completed over four hours. **(Level IV Evidence, Grade C Recommendation)**
  - NO signs of dehydration
     give maintenance therapy
  - Mild-moderate dehydration
     give 50-75 ml/kg ORS

Rehydration should be carried out under medical supervision and regular and frequent assessment of hydration status is essential. **(Level IV Evidence, Grade C Recommendation)** ORT may fail in children with continuing rapid stool loss (>10-20 ml/kg/hour), insufficient intake of ORS or frequent, severe vomiting.

Table 5   Oral rehydration solutions in Hong Kong

Product	Na	K	Cl	HCO₃	Citrate	Glucose	Other constituent	Rice	Osmolarity	Flavour	Form
ESPGAN guideline	60	20	60	-	10	74-111	-	-	200-250	-	-
G.E.S. 45	45	25	45	25	-	160	-	-	300	-	Sachet
ORS	90	20	80	-	10	111	-	-	311	Orange	Sachet
Pedialyte (plain)	45	20	35	-	10	139	-	-	249	-	Liquid
Pedialyte (flavoured)	45	20	35	-	10	111	Fructose:5	-	250	Fruit	Liquid
WHO-ORS B	90	20	80	30		111	-	-	331	-	Sachet
WHO-ORS C	90	20	80	-	10	111	-	-	311	-	Sachet
New WHO-ORS	75	20	65	-	10	75	-	-	245	-	Sachet
QMH Rice ORS	60	20	50	-	10	-	-	50	280	-	Liquid
Dioralyte	60	20	60	-	10	90	-	-	240	-	Sachet
Glucolyte	60	20	50	0	10	100	Gluconate 5	-	248	Regular, orange, apple	Sachet

Units : Electrolytes, citrate, glucose (mmol/L); Osmolarity (mosml/L); Fructose, rice (g/L)

(Level IV Evidence, Grade C Recommendation) If the child still has signs of dehydration at the end of four hours, appropriate rehydration therapy should be instituted accordingly.

- Maintenance fluids can be given as breast milk, formula, or other fluids appropriate for age, offered *ad libitum.* **(Level IV Evidence, Grade C Recommendation)** More fluids than usual should be offered to prevent dehydration. **(Level IV Evidence, Grade C Recommendation)** Drinks sweetened with sugar (e.g. soft drinks, sweetened juices) should be avoided as they may cause osmotic diarrhoea and hypernatraemia. **(Level IV Evidence, Grade C Recommendation)**

- Ongoing losses can be replaced by normal diets given ad libitum in children with mild diarrhoea and NO signs of dehydration. **(Level IV Evidence, Grade C Recommendation)** In high risk cases with persistent profuse diarrhoea or vomiting, ongoing losses should be replaced with extra feeds of low-sodium ORS (40-60 mmol/L of sodium). **(Level IV Evidence, Grade C Recommendation)** When high-sodium ORS (>60 mmol/L) is used to replace ongoing losses after rehydration, other low-sodium fluids (e.g. breast milk, formula, or water) should be given in alternate feeds. **(Level IV Evidence, Grade C Recommendation)** The following guide may be useful for caregivers to replace ongoing losses (stool and vomitus) during both rehydration and maintenance therapy: **(Level IV Evidence, Grade C Recommendation)**

Each watery or loose stool:

<2 years of age:	50-100 ml (¼ to ½ a large cup)
2-10 years:	100-200 ml (½ to 1 large cup)
OR	10 ml/kg

Each episode of emesis: 2 ml/kg

- Families should be advised to seek further medical advice should the child: **(Level IV Evidence, Grade C Recommendation)**
  - Starts to pass many watery stools
  - Has repeated vomiting
  - Becomes very thirsty
  - Is eating or drinking poorly
  - Develops a fever
  - Has blood in the stool
  - Deteriorates in any other way

Evidence

In the past many regimes aimed at gradual rehydration over 24 hours, but this approach was not evidence-based. Most authorities now recommend rapid rehydration over three to four hours.[42,45,46]

Management guidelines for the treatment of acute diarrhoea have been published by the WHO,[47] the Centers for Disease Control and Prevention,[42] and the American Academy of Paediatrics.[14] A recent evidence and consensus based guideline has been published in the United Kingdom,[13] and there is also a review article by Murphy.[48] In essence, the objectives of treatment are to prevent dehydration, treat dehydration and to prevent nutritional damage.

Vomiting

Recommendation

- ORT can successfully rehydrate most children even with vomiting. **(Level Ia Evidence, Grade A Recommendation)** Small volumes of ORS (5-10 ml) should be administered every 1-2 minutes, with a gradual increase in the amount consumed. **(Level IV Evidence, Grade C Recommendation)** Continuous, slow infusion of ORS via a nasogastric tube may be an alternative in non-comatose patients and those without ileus. **(Level III Evidence, Grade B Recommendation)**

Evidence

Greater than 90% of children who have vomiting and dehydration can be successfully rehydrated with ORT[25,49,50] when small volumes of ORS (5-10 mL) are administered every 1-2 minutes, with a gradual increase in the amount consumed. Continuous, slow nasogastric infusion through a feeding tube is another option in a child with frequent vomiting.[13,42]

Hypernatraemic Dehydration

Recommendation

- In hypernatraemic dehydration ORT is safer than intravenous rehydration. **(Level Ib Evidence, Grade A Recommendation)** Provided the child's neurological status is stable and the child is able to drink, use "Slow ORT", aiming to complete rehydration over 12 hours and monitoring serum sodium to avoid a rapid reduction. **(Level III Evidence, Grade B Recommendation)**

Evidence

In cases of hypernatraemia (serum sodium >150 mmol/L), "slow ORT" with fluid replacement over 12 hours has been recommended to reduce the risk of seizures.[51] None of 34 infants with hypernatraemic dehydration suffered seizures when rehydration was treated with WHO-ORS over 12 hours.[51] In another controlled trial of IV therapy versus ORT, 6% of hypernatraemic patients treated with ORT developed seizures compared with 25% in the group given intravenous treatment.[26]

Nutrition Therapy

Recommendation

- Breastfeeding should continue through rehydration and maintenance phases of treatment. **(Level Ib Evidence,**

Grade A Recommendation)

- Exclusive breastfeeding should be promoted to reduce the severity of acute diarrhoea in infants during the first six months of life. **(Level IIa Evidence, Grade B Recommendation)**
- Children who are not dehydrated should continue to be fed age-appropriate diets. **(Level Ia Evidence, Grade A Recommendation)**
- Dehydrated infants and children should be fed age-appropriate diets as soon as they are rehydrated (usually within 4 hours). **(Level Ia Evidence, Grade A Recommendation)**
- Gradual reintroduction of milk-based formulas or cow's milk is not routinely required. **(Level Ia Evidence, Grade A Recommendation)**
- Lactose free or lactose-reduced formulas are not routinely required. **(Level Ia Evidence, Grade A Recommendation)** They may be considered if there is no improvement in the stool consistency after several days or if reducing substances are identified in the stool. **(Level IV Evidence, Grade C Recommendation)**
- Complex carbohydrates (e.g. rice, wheat, potatoes, bread and cereals), lean meat, yoghurt, fruits, and vegetables are better tolerated and more preferred than foods which are sugary (e.g. tea, juices and soft drinks) or fatty. **(Level IV Evidence, Grade C Recommendation)**

Evidence

Although there has been a common belief that bowel rest would hasten the recovery of the bowel and decrease the severity and duration of the diarrhoea, there is evidence to the contrary. Early feeding may in fact decrease intestinal permeability changes induced by infection.[52] **(Level IIb Evidence, Grade B Recommendation)** Animal studies suggest it may also facilitate enterocyte healing and help maintain disaccharidase activity.[53] **(Level IIb Evidence, Grade B Recommendation)**

Evidence based guidelines on managing acute diarrhoea recommend that breastfeeding should continue through rehydration and maintenance phases of treatment of acute diarrhoea.[48,54] **(Level Ib Evidence, Grade A Recommendation)** The ESPGAN working group on acute diarrhoea recommended that at all times, breastfeeding should be continued.[55] **(Level IV Evidence, Grade C Recommendation)** It is noted that if a baby is being breast-fed at the time of a diarrhoeal episode, the progress of that episode is milder, particularly if breastfeeding is continued.[56-58] **(Level IV Evidence, Grade**

C Recommendation) Discontinuation of breastfeeding during diarrhoea significantly increases the risk of dehydration.[59] **(Level IIa Evidence, Grade B Recommendation)**

Clinical studies with a variety of early feeding regimens have demonstrated unrestricted diets do not worsen the course or symptoms of mild diarrhoea and can decrease stool output compared with oral rehydration therapy (ORT) or intravenous therapy alone.[54,58,60-66] **(Level Ib Evidence, Grade A Recommendation)** When used with ORT, early feeding can reduce stool output as much as cereal-based ORT can.[67,68] **(Level Ib Evidence, Grade A Recommendation)** Meta-analysis on the studies from developed countries shows that early refeeding reduces the duration of diarrhoea by 0.43 days (95% CI, -0.74 to -0.12), and improves nutrition.[14,63-65] **(Level Ia Evidence, Grade A Recommendation)** Currently early refeeding is recommended by the European Society of Paediatric Gastroenterology and Nutrition, the American Academy of Pediatrics and in a recent evidence and consensus based review.[13,14,55] **(Level IV Evidence, Grade C Recommendation)**

Lactose intolerance should be suspected in the presence of frothy watery acidic stools and with associated excoriation of the buttocks. Although transient lactase deficiency is common, particularly after rotavirus gastroenteritis, most children with decreased lactase levels do not have clinical features of malabsorption.[42] **(Level IV Evidence, Grade C Recommendation)** Clinically significant lactose intolerance secondary to acute diarrhoea is apparently uncommon in Europe.[69] **(Level IIb Evidence, Grade B Recommendation)** This has also been our experience on hospitalised children with acute diarrhoea in Hong Kong. **(Level IV Evidence, Grade C Recommendation)** A meta-analysis of clinical trials has indicated that lactose free diet is rarely necessary after acute diarrhoea.[70] **(Level Ia Evidence, Grade A Recommendation)** If children are followed up to identify the few in whom signs of malabsorption develop, a regular age-appropriate diet, including full-strength milk, can be safely used for refeeding.

The question of which foods are best for refeeding has been an issue of continuing study. Although agreement is not universal, controlled clinical trials suggest that certain foods, including complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meat, yoghurt, fruits, and vegetables, are better tolerated.[60,67,68,71] **(Level Ib Evidence, Grade A Recommendation)** Fatty foods or foods high in simple sugars (including tea, juices, and soft

drinks) should be avoided.[13,42] **(Level IV Evidence, Grade C Recommendation)**

Drug Therapy

Antibiotic Use

Recommendation
- Antibiotics are not recommended for uncomplicated diarrhoea. **(Level III Evidence, Grade B Recommendation)**
- Most cases of Salmonella gastroenteritis do not require antibiotic therapy as symptoms are not improved by antibiotics. **(Level Ib Evidence, Grade A Recommendation)**
- Parenteral antibiotics, e.g. third generation cephalosporins may be required for young infants (<3 months), any ill or septic looking patient and immunocompromised children with Salmonella gastroenteritis who have a higher risk of complications. **(Level IV Evidence, Grade C Recommendation)**
- *Campylobacter* gastroenteritis is usually self-limiting and antibiotic may only be of value if given early. Antibiotic may be indicated for children in institutional settings to shorten bacterial excretion. **(Level IV Evidence, Grade C Recommendation)**
- Shigellosis is highly infectious and notifiable. Antibiotic may shorten the infectious period but the disease is often self-limiting and hence antibiotic is used in ill patients or those who are still symptomatic when the pathogen is detected. **(Level IV Evidence, Grade C Recommendation)**
- Antibiotics are not usually required for diarrhoeagenic *E. Coli, Yersinia enterocolitica, Vibrio para-haemolyticus, Aeromonas spp., Plesiomonas spp.* Oral metronidazole or vancomycin is indicated for severe *Clostridium difficile* associated diarrhoea. Metronidazole is helpful for *giardia lamblia*. **(Level IV Evidence, Grade C Recommendation)**

Evidence

Salmonella

Salmonellosis is very common in Hong Kong. Randomised control trials have shown that antibiotic treatments, even with higher generation cephalosporins or macrolides, did not shorten the duration of diarrhoea or fever.[72] Antibiotics are not indicated, except for extra-intestinal involvement, immunocompromised patients, very

ill children, or infants younger than 3 months old.[16] Ampicillin, cefotaxime or ceftriaxone parenterally are useful in such situations.[16,73] Although local sensitivity patterns indicate that co-trimoxazole and chloramphenicol may also be effective,[74] they are seldom used as empirical therapy because of their potential side effects, especially in young infants.

Campylobacter

Campylobacter gastroenteritis is usually mild and self-limited. The benefit of antibiotic is questionable for the individual unless it is given within the first few days of the illness. However it shortens the period of bacterial shedding and hence may be useful for institutional children or nursery infants to reduce cross-infection.[75] Campylobacter spp. are sensitive to erythromycin and chloramphenicol.[74]

Shigella

Antibiotic therapy for shigellosis is controversial. Antibiotic is probably not needed in mild diarrhoea as the disease is often self-limited but it should be considered in severely ill patients and those who are still symptomatic when the stool culture is positive. It may shorten bacterial excretion.[75] The haemolytic uraemic syndrome (HUS) was associated with the use of antibiotics in shigella gastroenteritis. However, the risk of HUS may in fact be reduced if patients were given an appropriate antibiotic early. It is postulated that the inappropriate antibiotics, to which the bacteria are resistant, would allow the disease to progress or may even enhance the disease severity.[76] Nalidixic acid and ceftriaxone are usually effective.[74,75]

E. Coli

Diarrhoeagenic E. Coli are not a significant clinical problem locally.[77] Data on the use of antibiotics is limited.[78,79] There are six types: ETEC – Enterotoxigenic (traveller's diarrhoea and watery diarrhoea in weaning children); EPEC – Enteropathogenic (persistent watery diarrhoea in young children) where non-absorbable oral antibiotics, e.g., aminoglycosides, have been shown to be effective; EHEC – Enterohaemorrhagic (haemorrhagic colitis and HUS) where use of antibiotics is controversial; EIEC – Enteroinvasive (less severe invasive colitis); EAEC – Enteroaggregative (mucoid secretory acute or persistent diarrhoea); DAEC – Diffuse-adherent.

Other Bacteria

Yersinia enterocolitica, Vibrio parahaemolyticus, Aeromonas spp., and Plesiomonas spp. gastroenteritis are usually mild. Use of antibiotics is not necessary in general.[75] Staphylococcus aureus toxin causes vomiting and diarrhoea. Use of antibiotic is not indicated. Enteral symptoms caused by Bacillus cereus usually resolve within a day and do not require antibiotic.[75] Oral metronidazole or vancomycin is indicated for severe Clostridium difficile associated diarrhoea. A second course of these antibiotics and/or probiotics may be helpful to treat relapse, which may be up to 40%.[75,80]

Parasites

Giardia lamblia and Entamoeba histolytica very occasionally cause diarrhoea. Metronidazole is helpful.[81,82]

Probiotics

Recommendation

- Probiotics (Lactobacillus) are safe and effective and can be recommended for the treatment of children with acute infectious diarrhoea. **(Level Ia Evidence, Grade A Recommendation)**

Evidence

Microflora of the large intestine normally ferment residual carbohydrate and produce short chain fatty acids (SCFAs). This reduces the luminal pH and discourages intestinal pathogens. The SCFAs also enhance colonic water absorption. In acute diarrhoea, as intestinal microflora is altered, production of SCFAs is reduced and there is increased water loss.[14] Given these theoretical advantages, probiotics have been tried on acute infectious diarrhoea.[83] Among the probiotics, Lactobacillus spp. and Saccharomyces boulardii are more widely studied and used clinically. Still the number of studies for treatment of acute diarrhoea is small. The evidence that Lactobacillus spp. alter the course of diarrhoea is not consistently demonstrated.[14] Saccharomyces boulardii is a non-pathogenic yeast and was found to be effective in the treatment of diarrhoea associated with Clostridium difficile.[84] One randomised placebo-controlled study demonstrated its efficacy in shortening the duration of acute childhood diarrhoea.[85] A recent meta-analysis suggests that Lactobacillus is safe and effective as treatment for children with acute infectious diarrhoea.[86] Issues of cost effectiveness need further investigation to better delineate the role of probiotics in management of acute diarrhoea (Table 6).

Table 6   List of Probiotics in Drugdex and Martindale from HALIS search and MIMS (Hong Kong)

Brand names	Micro-organisms
Bacid	*Lactobacillus*
Bioflor*	*Saccharomyces boulardii*
DDS-Acidophilus	*L. acidophilus*
Enpac	*Lactobacillus*
Infloran Berna*	*Bifidobacterium infantis, Lactobacillus acidophilus*
Lacteol fort*	*L. acidophilus (killed)*
Lactinex	*L. acidophilus + L. bulgaris*
Shin-Biofermin S*	*Bifidobacterium bifidum, Lactobacillus acidophilus, Streptococcus fecalis*

*available in Hong Kong

Antidiarrhoeal Agents

Recommendation

- Antidiarrhoeal drugs are not routinely recommended for acute diarrhoea in children. **(Level IV Evidence, Grade C Recommendation)**
- These agents should not be used in children with fever, toxaemia or blood in the stool. **(Level IV Evidence, Grade C Recommendation)**
- Users of these agents as adjunctive therapy should pay attention to precautions and possible risks. Attention to the appropriate dosage and proper education of parents are prudent. **(Level IV Evidence, Grade C Recommendation)**

Evidence

Anti-motility Drugs

Examples of these drugs include loperamide, diphenoxylate + atropine, difenoxin & atropine, paregoric. These drugs act rapidly by producing segmental contractions of the intestine, thereby reducing peristalsis, diarrhoea and pain. They may also inhibit intestinal secretion. Side effects include dizziness, dry mouth, drowsiness, constipation & vomiting. They should be avoided in patients with high fever, toxaemia, or bloody mucoid stools.[87] They are usually not necessary for the management of acute diarrhoea as it is usually self-limiting. Most are not approved for children less than 2 or 3 years of age.[88] In certain circumstances, they may be used as an adjunctive treatment to oral rehydration therapy. These

drugs should only be prescribed to children of appropriate age group and with the recommended dosage. Parents should be routinely reminded the directions of dosing and the possible side effects.

Results of clinical trials on loperamide are too conflicting to allow any conclusion about the risk benefit ratio. Seven placebo-controlled trials with loperamide were identified and four showed either an antidiarrhoeal effect or better weight gain in the loperamide group,[87,89-91] while the other studies found no benefit.[92-94] However, side effects were associated with loperamide use, especially with the higher dose of 0.4-0.8 mg/kg/day.[91] The most recent study that demonstrated benefit with minimal side effects used a dose of 0.14-0.28 mg/kg/day in children 2 years or more.[87]

Loperamide is approved by U.S. Food and Drug Administration for treating acute diarrhoea only in patients at or above 2 years old. Diluted syrup form may be safer than concentrated drops as the chance of overdose for the latter preparation is probably higher. The risk of inadvertent overdose is a concern.[95] The American Academy of Pediatrics does not recommend loperamide to treat acute diarrhoea in children based on strong committee consensus and limited scientific evidence that the risks of adverse effects outweigh the limited benefits.[14]

Loperamide has often been used by paediatricians locally as reported in a recent retrospective questionnaire survey.[96] The Private Practising Paediatricians Study Group recommended the following dosage for loperamide: ≤0.1 mg/kg/dose three times a day as required. The diluted preparation rather than loperamide drops were recommended and only limited doses per visit should be given.[96]

Adsorbents

Examples of these drugs include smectite, kaolin-pectin, attapulgite. These theoretically act by adsorbing bacterial toxins and binding water to improve stool consistency. They may also adsorb nutrients, enzymes and medications in the intestine.[88] Although a few controlled studies have shown possible benefit,[97-101] most medical authorities still do not think the evidence is convincing enough for recommending their routine use.[14,82,102] Passage of a formed stool does not imply therapeutic success because water content can remain high in such "formed" stools. Such cosmetic changes may give patients or their families a false sense of security, causing a delay in seeking more effective treatment. Therefore careful explanation to parents is needed when prescribing these drugs.

Anti-secretory Drugs

Examples of these drugs include bismuth-subsalicylate and racecadotril. Bismuth subsalicylate has been used as adjunctive therapy for acute diarrhoea. The mechanism of action is uncertain. It may act by inhibiting intestinal secretion. It was shown to reduce the frequency of unformed stools and decreased stool weight. No side effect was reported with the dosage of 100-150 mg/kg/day.[103,104] However, the beneficial effects have been modest. As systemic absorption was noted, Reye syndrome is a theoretical risk.[105] Racecadotril (synonyms: acetorphan, ecatorfate) inhibits enkephalinase to exert its anti-secretory effect by prolonging the action of endogenous enkephalins. It has a potential application in acute diarrhoea but studies are too few for any recommendation at present.[106,107]

In summary, all of the above drugs are not routinely needed because of lack of convincing clinical benefit while hydration therapy is well established. However individualised use as adjunctive therapy is sometimes useful while paying attention to the possible risk and precautions.[14,82]

Acknowledgements

Tables of Evidence

Table A   Assessment of dehydration

Authors	Study design	N	Treatment	Results/Comments
(Gorelick et al, 1997)[9] Philadelphia	Prospective cohort 1 m-5 yr	186	Evaluated for 10 clinical signs before treatment Fluid deficit determined from serial weight gain after treatment	Capillary refill >2 seconds, absent tears, dry mucus membrane, and general appearance predict dehydration, indicate a deficit of at least 5%.
(Mackenzie et al, 1989)[10] Australia	Prospective cohort <4 yr	102	Evaluated for presence of any or obvious sign of dehydration according to hospital guideline	The mean estimated dehydration was 6.6% and the mean true dehydration was 3.4%. 3-4% is the level at which dehydration becomes clinically apparent, rather than 5% as usually stated. Decreased skin turgor is the earliest sign of dehydration. Signs that pointed to dehydration >4% are: acidotic breathing, decreased peripheral perfusion, decreased skin turgor.
(Duggan et al, 1996)[11] Egypt	Prospective cohort 3-18 m	135	Clinical assessment of signs according to two guidelines: Santosham & Fortin and Parent	Patients classified as having mild, moderate and severe dehydration were found to have ~4%, ~5% and ~10% gain in percent weight respectively. Abnormal skinfold is most significantly correlated with degree of dehydration followed by neurological status, weak pulse, sunken eyes, dry mucous membranes, deep breathing, weak pulse and cold extremities.

Yr – years; m – months

Table B   Investigations

Authors	Study Design	N	Results/Comments
(Anonymous, 1996)[14]	Expert committee opinions	93 ref	Electrolyte levels should be checked in moderately or severely dehydrated children as well as those on intravenous drip. Knowledge of electrolyte levels is especially important in hypernatraemic dehydration.
(Meropol et al, 1997)[15] U.S.A.	Retrospective descriptive study	250 hospital admissions; 3-18 years old	Band neutrophil count of 0.1×10^9/L is 100% sensitive but not specific in picking up patient with positive stool bacterial cultures. (positive predictive value 9%, negative predictive value 100%) Only 7 of 250 (2.8%) admitted patients have positive stool bacterial culture.
(Geme et al, 1988)[16]	Consensus opinions and non-systematic review	32 ref	The need of a blood culture for young infant with diarrhoea follows the principles as for other acute infectious illnesses. However, if *Salmonella* is suspected for epidemiological reasons, blood culture is needed even if the infant is not very ill as *Salmonella* bacteraemia is frequent and clinical severity of illness is a poor predictor for bacteraemia in infants with *Salmonella* gastroenteritis. Immunocompromised children are more likely to have extra-intestinal *Salmonella* infections.
(Gastanaduy & Begue, 1999)[17]	Non-systematic review	42 ref	In developed countries, percentage of positive bacterial stool cultures and parasite detection are as follows: - *Salmonella sp.: 2-4; Campylobacter sp.: 1-7; Shigella sp.: 1-3; Enterotoxigenic E. coli: 1-4; Aeromonas sp.: <1; Vibrio sp.: rare; Giardia lamblia: 0-8; Cryptosporidium parvum: 1-3; Entamoeba histolytica: rare.*
(Biswas et al, 1996a)[2] Hong Kong	Prospective case-control study	388 hospitalised children with diarrhoea: birth-15 years old (95% are <5 years old); 306 control children	Bacterial stool cultures were positive in 30% of diarrhoea patients versus 5.6% of controls. Rotavirus was detected in 130 cases with diarrhoea (34%). *Giardia lamblia* cysts were found in 1 case only (0.3%).
(Kwan et al, 1999)[18] Hong Kong	Retrospective descriptive study	2800 stools from 1135 hospitalised children	Excluded immunodeficiency, routine stool surveillance and rectal swabs. 21.7% of patients yielded bacterial pathogens; 95.1% of cases were picked up by the first stool specimen; a second and third specimen increased the yield to 98.4% and 99.1% respectively.
(Huicho et al, 1996)[19] Various overseas studies analysed	Meta-analysis	2603 ref identified, 81 was relevant and 25 were fit for analysis	Among the faecal screening tests, faecal lactoferrin was the most accurate index test for inflammatory bacterial diarrhoea; faecal occult blood produced intermediate performance while faecal leukocytes was the poorest index test.
(Chan et al, 1994)[3] Hong Kong	Retrospective descriptive study	Database of Virus Unit of Department of Health 1987-1992	For children 0-5 years old with acute diarrhoea, of 24466 stool specimens received, 4086 (16.7%) yielded viruses that might cause gastroenteritis: Rotavirus: 3462; Adenovirus: 386; Astrovirus: 151; Norwalk-like: 71; Calicivirus: 16.

Table C (1)   Randomised, controlled trials of ORT and IV rehydration in developed countries (Level I)

Authors	Study design	n	Treatment	Results/Comments
(Santosham et al, 1982)[23] U.S.A. & Panama	RCT 52 in US, 94 in Panama	98 ORT(50 GpA, 48 GpB) 48 IV	ORSA - WHO-ORS ORSB - Na 50, Cl 40, osmolarity 251 Rehydrate over 12 h Dilute soya formula when diarrhoea stopped	Rotavirus main pathogen 97/98 ORT successful (from Gp A). All patients with electrolyte disturbances were successfully treated. All 6 with hypernatraemia successfully rehydrated with ORT alone (4 Gp A, 2 Gp B).
(Bhargava et al, 1984)[27] India	RCT Birth to 3 m	22 ORSA 22 ORSB 21 IV	ORSA - WHO-ORS ORSB - Na 60, Cl 50, osmolarity 270 Rehydrate over 8 h Full feeding when diarrhoea stopped	44/44 ORT successful Dehydration, acidosis, electrolyte disturbances corrected with equal efficacy in all 3 groups
(Sharifi et al, 1985)[26] Iran	RCT	236 ORT 234 IV	Rehydration ORS: Na 80, HCO 35, Cl 65, G 70, osmolarity 270, at 40 ml/kg/hr via NGT Maintenance ORS: Na 40, K30, G1 30, HCO 25, Cl 45, osmolarity 270 Refeed small amount of normal diet within 24 h	235/236 ORT successful. ORT associated with lower incidence of convulsion in hypernatraemic patients, lower incidence of iatrogenic electrolyte disturbances, shorter duration of diarrhoea, greater weight gain and more rapid correction of hypokalaemia & acidosis.
(Tamer et al, 1985)[24] U.S.A.	RCT	47 ORT 50 IV	ORS with Na 75, K75 for 6 h followed by ORS with Na 50, K50 Dilute soya formula after rehydration	44/47 ORT successful. ORT associated with faster correction of acidosis and sustained rise in potassium.
(Listernick et al, 1986)[49] U.S.A.	RCT Outpatient	15 ORT 14 IV	ORS : Na 60, K 20, Cl 50, citrate 30, G 111, fructose 28; 20 ml/kg 1st hour, then ad lib ½ strength lactose-free formula after 24 h	Rotavirus main pathogen. History of vomiting in 100%. 13/15 successfully rehydrated with ORS. 2 failed – persistent vomiting and UTI. No difference in electrolytes.
(Vesikari et al, 1987)[25] Finland	RCT	22 ORT 15 IV	Rapid IV (12 hours) versus ORT ORS : Na 60, K 20, Cl 50, $HCO_3$30, G 144, rehydrated over 6 h Normal diet after 12 hours	Rotavirus main pathogens. 2 in ORT required IV supplements. Correction of dehydration, metabolic acidosis and sodium deficit at equal rates. Duration of diarrhoea shorter in ORT. Better reintroduction of feeding in ORT.
(Mackenzie & Barnes, 1991)[50] Australia	RCT Stratified by age	52 ORT 52 IV	ORS : Na 50, K 20, Cl 40, citrate 10, G 111 Rehydrated over 6 h orally/ nasogastric tube IV : deficit replaced over 24 h No solid during rehydration	Rotavirus main pathogen. 3.8% failure rate in ORT group. Higher percentage with vomiting. No difference in number of stool passed in first 24 h. None had electrolytes and acid base disturbances.
(Issenman & Leung, 1993)[108] Canada	RCT	42	ORS : Na 75 and 45	Successful in 82% for ORT and 78% for IV.

RCT – Randomised controlled trial

All concentrations given in mmol/L.

Table C (2) Randomised, controlled trials comparing WHO-ORS with hypotonic ORS (Level I)

Authors	Study design	n	Treatment protocol	Results/Comments
(Bhargava et al, 1984)[27] India	RCT Birth to 3 m 3 cells with IV arm	22 (WHO) 22 (HORS) 21 (IV)	HORS (Na 60, Cl 50, osmolarity 270) Rehydrate over 8 h Full feeding when diarrhoea stopped	Dehydration, acidosis, electrolyte disturbances corrected with equal efficacy. HORS associated with lower mean Na, less patients with hypernatraemia, irritability & convulsion.
(el Mougi et al, 1994)[109] Egypt	RCT 3 cells with IV arm	20 (HORS) 21 (WHO) 20 (IV)	HORS (Na 60, Cl 75, K 13, Cl 53, citrate 6.6, osmolarity 210). Plain water allowed after rehydration for WHO group. Normal diet after 4-6 h	HORS associated with lower fluid intake, lower stool output and a trend towards shorter duration of diarrhoea versus WHO-ORS. Serum sodium decreased by 2.9 mmol/L but within normal range.
(Mahalanabis et al, 1995)[110] Bangladesh	RCT	30 (HORS) 30 (WHO)	HORS (Na 67, G 89, Cl 66, citrate 7, osmolarity 249). Rotavirus and *E. Coli* main pathogens. 30% undernourished	HORS associated with lower ORS intake and lower stool output in non-rotavirus group. No difference in electrolytes.
(Santosham et al, 1996)[111] Egypt	RCT	94 (HORS) 96 (WHO)	HORS (Na 75, G 75, Cl 65, osmolarity 245) Pre-cooked rice vegetable mixture after rehydration (<12 h)	HORS associated with lower stool output (36%) and lower risk of vomiting during rehydration and lower risk of treatment failure. No difference during maintenance phase. Ris of development or worsening of hyponatraemia not increased in HORS
(Valentiner-Branth et al, 1999)[112] West Africa	RCT Community based	344 (HORS) 361 (WHO)	HORS (Na 60, G 84, Cl 50, osmolarity 224) *E. Coli* main pathogens	HORS as efficacious in terms of duration of diarrhoea and stool output. HORS associated with shorter duration of diarrhoea and lower stool output in Non-breast-fed toddlers.
(CHOICE Study Group, 2001)[35] Multicentre in 5 countries	RCT	341 (HORS) 334 (WHO)	HORS (Na 75, G 75, osmolarity 245)	33% reduction in unscheduled IV therapy No difference in stool output, duration of diarrhoea and % vomiting. No significant difference in incidence of hyponatraemia.

RCT – Randomised controlled trials, HORS – Hypotonic ORS, WHO – WHO-ORS

All concentrations given in mmol/L. Electrolytes concentration same as WHO-ORS unless otherwise specified

Table C (3) Clinical trials comparing High osmolarity ORS with low osmolarity ORS

Authors	Study design	n	Treatment	Results / comments
(Rautanen et al, 1993)[113] Finland	Non-randomised Open trial	103 (HORS) 135 (SORS)	HORS (Na 60, G 84, Cl 50, osmolarity 224) SORS (Na 60, Cl 50, G 144, HCO 30, osmolarity 304). Rehydrate over 6-8 h orally/ nasogastric tubes (2x deficit). Normal diet after rehydration. Rotavirus in >75% of cases	HORS associated with lower stool output, shorter duration of diarrhoea and hospitalisation and less ORS intake. Requirement for IV supplementation not different.
(Rautanen et al, 1997)[114] Finland	RCT	35 (HORS) 35 (SORS)	Same as 1 Rehydration over 6-8 h = 4/3 vol of deficit Normal feeding after rehydration Rotavirus in 57%	HORS associated with lower stool output and lower ORS intake. No difference in weight gain, electrolyte balance, recovery from acidosis and requirement for IV therapy. Subgroup analysis for rotavirus infection showed similar beneficial effect of HORS.

RCT – Randomised controlled trial, HORS – Hypotonic ORS, SORS – Standard ORS

Electrolyte concentrations same as WHO-ORS unless otherwise specified

Table C (4)   Rice-based ORS versus WHO-ORS (Level I)

Authors	Study design	n	Treatment	Results/Comments
(Patra et al, 1982)[115] India	RT, unblinded 3 m-5 yr Failure excluded	26 (RORS) 26 (WHO)	RORS – pop rice-based 50 g Fed ad lib	Cholera and rotavirus main pathogens. RORS associated with lower stool output and ORS intake and shorter duration of diarrhoea.
(Molla et al, 1985)[116] Bangladesh	RT, unblinded 157 adults and 185 children	84 (RORS) 101 (WHO)	RORS – 80 g, osmolarity 288	75% severe dehydration, 75% cholera infection. RORS associated with lower stool output, lower ORS intake and lower failure rate.
(Alam et al, 1987)[117] Bangladesh	RT, unblinded 3-cell study 1-8 yr Failure excluded	24 (RORS) 24 (WORS) 24 (WHO)	RORS – 50 g rice powder WORS – 50 g wheat powder, osmolarity 280. IV for 1-2 h Normal diet after rehydration	Cholera main pathogen. RORS and WORS associated with lower stool output and ORS intake. Same failure rates, same duration of diarrhoea. No difference in non-cholera subgroup.
(Bhan et al, 1987)[118] New Delhi	RT, unblinded 3-cell study 3 m-5 yr	31 (RORS) 29 (LORS) 33 (WHO)	RORS – 50 g pop rice powder LORS – 60 g Mung bean powder Rehydrate over 8 h ½ milk after 8 h cereal after 24 h	Rotavirus and *E. Coli* main pathogens. No difference in failure rates, purging rates, duration of diarrhoea, changes in electrolytes and presence of reducing substances. RORS associated with higher urine output and intake of solid foods.
(Dutta et al, 1988)[119] Calcutta	RT, unblinded 3-cell study 4 m-4 yr	35 (RORS) 37 (PRORS) 33 (WHO)	RORS – 30 g rice powder (RORS) and 50 g pop rice powder (PRORS) ½ milk and BF after 6 h	Cholera, *E. Coli* and rotavirus main pathogens No difference in stool output, duration of diarrhoea, ORS intake and weight gain.
(el Mougi et al, 1988)[120] Egypt	RT, unblinded 4-18 m	30 (RORS) 30 (WHO)	RORS – 50 g rice powder ½ milk after 6 h for 24 h, then FS milk	Stool cultures not done. Children mildly malnourished. RORS associated with better weight gain, shorter duration of diarrhoea, lower ORS intake and stool output and less episodes of vomiting Same failure rates.
(Mohan et al, 1988)[121] New Delhi	RT, unblinded Failure excluded	26 (RORS) 24 (WHO)	RORS – 50 g rice powder ½ milk and normal diet after 8 h	80% had vomiting. Failure rate same. RORS associated with decreased stool frequency in 1st 24 h.
(Molla et al, 1989)[122] Bangladesh	RT, unblinded <5 yr	47 (RORS) 46 (WHO)	RORS – 50 g rice-flour based Normal diet after 24 h	Cholera proven cases only. RORS associated with lower ORS intake and stool output in 1st 24 h only.
(Fayad et al, 1993)[67] Egypt	RT, unblinded 3-18 m	219 (RORS) 222 (WHO)	RORS – pre-cooked rice-based 50 g Weaning diet after rehydration (4-12 h)	No differences in rehydration phase in stool volume, ORS intake, weight gain and duration of rehydration. WHO-ORS associated with lower stool volumes and ORS intake and shorter duration of diarrhoea after initiation of feeding. Failure rates same. Duration of diarrhoea on admission longer in WHO group by 1 day.

Table C (4)   Rice-based ORS versus WHO-ORS (Level I) (con't)

Authors	Study design	n	Treatment	Results/Comments
(Islam et al, 1994)[123] Pakistan	RT, unblinded	27 (RORS) 25 (WHO)	RORS – 50 g rice powder, osmolarity 288 Infants <6 months old Normal diet after 6 h (1/2 S milk)	*E. Coli* most common pathogen. Success rate: RORS 70%, WHO 72%. RORS associated with lower stool output and ORS intake from 6-48 h, no difference in duration of diarrhoea and presence of glucose intolerance.
(Maulen-Radovan et al, 1994)[124] Mexico	RT, unblinded	49 (RORS) 48 (WHO)	RORS – pre-cooked rice-based 50g Infants <6 months old. Low-protein milk and FS milk after 6 h for infants below or above 4 m	Rotavirus and *E.Coli* main pathogens. No difference in stool output, ORS intake, duration of diarrhoea, presence of reducing substances in stool.
(Guiraldes et al, 1995)[125] Chile	RT, unblinded 3-18 m	51 (RORS) 49 (WHO)	RORS – pre-cooked rice powder 50 g, osmolarity 260. ORS only 1st 4 h, then plain water added next 2 h, normal diet after 6 h	Rotavirus and *E. Coli* main pathogens. No differences in stool output, duration of diarrhoea, carbohydrate malabsorption and failure rates.
(Dutta et al, 2000)[126] Calcutta	RT, 2-10 yr, boys	19 (HORS) 19 (RORS) 20 (WHO)	HORS – Na 70, K 20, G 16.2, RORS – Na 70, K 20, rice 50	All cholera. All patients given IV therapy for first 6-8 h and treated with tetracycline for 3 days. Duration of diarrhoea, stool output and ORS requirement all significantly less in rice-ORS.
(Zaman et al, 2001)[127] Bangladesh	RT, unblinded 5-15 yr, boys	85 (RORS) 82 (WHO)	RORS – Packaged proprietary form of rice syrup 40 g, Na 90, osmolarity 270	88% had cholera, all given antibiotics and early feeding. Stool output decreased by 20% in rice-ORS in first 8 h only.

RORS – Rice-based ORS, PRORS – Pop rice powder ORS, LORS – Lentil based ORS, WORS – Wheat-based ORS, WHO – WHO-ORS, HORS – Hypotonic glucose ORS, RT – Randomised trials, Yr – years, m – months

Rice concentration – in g/L

Other concentrations given in mmol/L

RORS – same electrolyte concentrations as WHO-ORS unless otherwise specified

Table D   Nutrition therapy

Authors	Study design	n	Treatment	Results/Comments
(Alarcon et al, 1991)[60] Developing country	RCT	29:28:28	Soy formula, wheat-peas, potato-milk	Latter two locally available diets were as effective as commercial soy formula.
(Anonymous, 1996)[14]	Review/Meta	93 ref		AAP guidelines on management of acute gastroenteritis in young children.
(Brown et al, 1988)[61] Developing country	RCT	31:29:34:34	4 lactose free groups	Malnourished. Therapeutic success similar in 4 groups (lactose free). Continued early oral feeding improved nutritional results.
(Brown et al, 1991)[71] Developing country	RCT	28:30:29:29	Milk-noodles and milk	Two noodle-milk groups better than two milk groups.
(Brown & Lake, 1991)[58]	Review	49 ref		Continue feeding during diarrhoea; excess complications in small subgroup with exclusive nonhuman milk; discuss methodological problems.
(Brown et al, 1994)[70]	Meta	43 ref		Vast majority of young children with acute diarrhoea successfully managed on undiluted nonhuman milks. Routine use of lactose-free milk is unnecessary.
(Duggan et al, 1992)[42]	Review			CDC guidelines on management of acute gastroenteritis.
(Faruque et al, 1992)[59] Developed country	Case-control	285:728		Withdrawal of breastfeeding during diarrhoea 5x increase risk of dehydration.
(Fayad et al, 1993)[67] Developing country	RCT	222:210	G-ORS and R-ORS	G-ORS resulted in lower stool volumes than R-ORS after early introduction of rice diet.
(Fox et al, 1990)[62] Developing country	RCT	32:30	Gradual versus abrupt refeeding	Gradual refeeding versus abrupt refeeding in infants under 6 months. No difference but 42% had diarrhoea recurrence responding to lactose-free formula.
(Golding et al, 1997)[56]	Review	61 ref		Focus on breastfeeding and protection against gastroenteritis.
(Hjelt et al, 1989)[63] Developed country	RCT	25:27	Gradual versus rapid refeeding with full-strength lactose-limited milk.	Higher stool frequency and energy intake in rapid group.
(Isolauri & Vesikari, 1985)[64] Developed country	RCT	11:42:39	IV fluids, WHO ORS or low osmolality ORS groups, also randomised to receive cholestyramine or placebo, and randomised to rapid or slow feeding schedule	Rapid feeding group did better.
(Isolauri et al, 1989)[52] Developed country	Comparative	50 (41)	Grouping (parents preadmission treatment): A (n=12) fasted; B (n=17) oral fluids; C (n=12) fluids + food	

Table D   Nutrition therapy (con't)

Authors	Study design	n	Treatment	Results/Comments
(Khin et al, 1985)[54] Developing country	RCT	26:26	Breastfeeding continued or not	Continued breastfeeding group during diarrhoea passed fewer stools of smaller volume and recovered quicker.
(Lembcke & Brown, 1992)[57]	Review	29 ref		Continue breastfeeding (2 ref); also feeding in most cases; exclusive non-human milk may increase complications.
(Levine et al, 1974)[53]	Animal	6/7		IV alimentation versus oral – effect on gut mucosa.
(Margolis et al, 1990) Developed country[65]	RCT	21:35	Unrestricted diet versus graded refeeding	Children with mild diarrhoea on unrestricted diet recovered sooner than infants given graded refeeding.
(Murphy, 1998)[48]	Review	70 ref		Guidelines based on systematic review.
(Rees & Brook, 1979)[66] Developed country	RCT	16:16:14	Full-strength (FS), clear fluids (CF) + FS or CF + graded refeeding	More vomiting in FS but no need to change treatment.
(Sandhu et al, 1997)[69] Developed country	RCT	134:96	Early and late feeding groups in multicentre study	
(Santosham et al, 1990)[68] Developing country	RCT	50x4	G-ORS/Soy Formula, G-ORS/Rice Formula, R-ORS/SF, G-ORS/rice	
(Walker-Smith et al, 1997)[55]	Review	14 ref		ESPGAN recommendations for feeding in childhood gastroenteritis.

Table E   Antibiotic use

Authors	Study design	n	Treatment	Results/Comments
(Nelson et al, 1980)[128] U.S.A.	Prospective randomised double-blind placebo control study	Paediatric patients:- Ampicillin group: n=15 Amoxicillin group: n=15 Placebo group: n=14	Ampicillin or amoxicillin 100 mg/kg/day in 4 divided doses x 5 days or placebo x 5 days	No difference in duration of diarrhoea among the 3 groups. Bacteriologic relapse was higher in antibiotic group (p=0.003).
(Chiu et al, 1999)[72] Taiwan	Prospective randomised control study	42 children >6 months old with uncomplicated *Salmonella* gastroenteritis, equally divided among 3 groups	Oral macrolide and third generation cephalosporin therapy were studied: A: Azithromycin 10 mg/kg/day once daily x 5 days; B: Cefixime 10 mg/kg/day bd. x 5 days; C: No antibiotic	Duration of fever, diarrhoea and *Salmonella* carriage were similar in the three groups.
(Aserkoff & Bennett, 1969)[129] U.S.A.	Cohort study at an outbreak of *Salmonella typhimurium*	Antibiotic treated: n=185 No antibiotic: n=87 All were symptomatic adults	Ampicillin 1 g daily x 3 days or Chloramphenicol 1 g daily x 3 days	65.4% and 27.0% of antibiotic treated patients still carried *Salmonella* 12 and 31 days respectively after exposure compared to corresponding figures of 42.5% and 11.5% for those not given antibiotics.
(Geme et al, 1988)[16]	Consensus opinions and non-systematic review	32 ref	Discussion on investigations and antibiotic treatment for infants with *Salmonella* gastroenteritis in developed country (U.S.A.)	Antibiotic therapy is not needed in children with uncomplicated *Salmonella* gastroenteritis in general. Bacteraemia and extraintestinal complication is more likely in young infants, especially those <3 months old. Any infant with *Salmonella* gastroenteritis should have a blood culture done. If *Salmonella* bacteraemia is documented or if the infant is ill, he should be treated with cefotaxime or ceftriaxone. Immunocompromised patients should receive antibiotics even if they do not appear ill.
(Anonymous, 2000)[130]	Expert committee opinions and non-systematic review	Not listed	Discussion on treatment of infections for developed country (U.S.A.)	Treatment of individual infectious diarrhoea is discussed.
(Pickering & Matson, 1995)[73]	Expert opinions and non-systematic review	197 ref	Treatment modality for infectious diarrhoea in children	Antibiotic choices and dosages for various bacterial and parasitic causes of diarrhoea are discussed. Of note is dosage intervals for cefotaxime, ceftriaxone and ampicillin in treating *Salmonella* bacteraemia are every 6, 12 and 4 hours respectively.

Table E   Antibiotic Use (con't)

Authors	Study design	n	Treatment	Results/Comments
(Cohen & Laney, 1999)[75]	Expert opinions and non-systematic review	249 ref		Antibiotic therapy for various bacterial pathogens were discussed. For *Campylobacter* gastroenteritis, bacterial excretion may be up to 7 weeks; this may be shortened by antibiotic therapy. Antibiotic may also shorten symptomatic period if given within 4 days of the illness. Antibiotics neither reduce symptoms nor shorten bacterial excretion period for *Yersinia* gastroenteritis. Antibiotic is recommended only if patient has severe disease and underlying illness. Similarly, antibiotic is advised for severe cases of gastroenteritis due to *Vibrio parahaemolyticus, Aeromonas* and *Plesiomonas.*
(Butler et al, 1987)[76] Bangladesh	Retrospective case control study	30 children of haemolytic-uraemic syndrome (HUS) and 30 age-matched control subjects; all had *Shigella dysenteriae 1* isolated	Antibiotic treatment was started empirically for all patients on the first day of admission	14 cases of HUS group vs. 6 of control group had received antimicrobial therapy before admission (p<0.05); inappropriate antibiotic use in first 2 days after admission was found in 17 cases in HUS group vs. 7 in control group (p<0.05).
(Nataro & Kaper, 1998)[78]	Non-systematic review	719 ref	Not applicable	It was a comprehensive review on diarrhoeagenic *E. Coli*. Both the microbiological and clinical aspects were covered.
(Wong et al, 2000)[79] U.S.A.	Prospective cohort study	N=71	History of treatment, both antibiotic or non-antibiotic, were reviewed for each patient	Children with *E. Coli* O157:H7 were studied. Antibiotics increased the risk of HUS: HUS occurred in 5 of 9 children (56%) who were given antibiotics versus 5 of 62 (8%) who did not receive antibiotics (p<0.001).
(Vanderhoof & Young, 1998)[84]	Non-systematic review	121 ref	Probiotic therapy for children	Use of probiotics for *Clostridium difficile* associated diarrhoea was discussed.
(Pruksananonda & Powell, 1989)[80] U.S.A.	Case report and non-systematic review	N=2 (4 months and 1 year old respectively)	Cholestyramine therapy x 7 weeks was effective for relapse of *Clostridium difficile* associated diarrhoea	Cholestyramine was efficacious in the two cases.
(Heresi & Cleary, 1997)[81]	Expert opinions and non-systematic review	10 ref (for reader)	Treatment of giardiasis	Quinacrine, furazolidone and metronidazole were listed as effective therapy but FDA only approved the first two for children since it consider the safety of metronidazole in children being uncertain in view of its mutagenic effect in animals.
(WHO, 1990)[82]	Expert opinions and non-systematic review		Treatment of giardiasis and amoebiasis	Metronidazole is listed as drug of choice for both conditions; alternatives for giardiasis are tinidazole, ornidazole and quinacrine; alternative therapy for amoebiasis is dehydroemetine hydrochloride.

Table F (1)   Drug therapy: Loperamide

Authors	Study design	n	Treatment	Results/Comments
(Motala et al, 1990)[91]	Placebo-controlled	30 infants (male, 6 wk-12 m), 30 control	Loperamide 0.8 mg/kg/day	Subjects: shorter duration of diarrhoea (2.5 vs 6 days) Lower daily stool output (gm/dg/day) No difference in rotavirus GE 4 drowsiness, 1 ileus, 1 persistent severe vomiting, doubts regarding safety.
(Bowie et al, 1995)[92]	Double-blind Placebo-controlled	91 infants & young children, 94 control acute dehydrating diarrhoea		No difference between groups for duration of rehydration or no. of treatment failures. Use of loperamide not recommended.
(Anonymous, 1984)[89]	Double-blind Placebo-controlled Multicentre	315 young children	0.4 mg/kg/day, 0.8 mg/kg/day or placebo	Larger proportion of children in Loperamide groups gained wt than in placebo (wt on admission & 3 days later) 1 abdominal distension.
(Karrar et al, 1987)[90]	Double-blind Placebo-controlled	53 young children	0.4 mg/kg/day, 0.8 mg/kg/day or placebo	Recovery rate p<0.05 Fastest: 0.8 mg/kg/day Slowest: placebo gp Wt gain (on admission & 3 days later) Loperamide gps > placebo p<0.05 1 excessive lethargy & sleepy
(Ghisolfi et al, 1987)[93]	Double-blind Placebo-controlled	63 infants 1-32 m	Loperamide 0.16-0.2 mg/kg/day	No significant decrease in no. of stools or more rapid recovery from diarrhoea. No mention of side effect.
(Owens et al, 1981)[94]	Double-blind Placebo-controlled	50 subjects 1 m-4 yr	Loperamide 0.2 mg/kg/day	No significant difference in duration of diarrhoea. No side effect.
(Kaplan et al, 1999)[87]	Multicentre randomised controlled-placebo	130 subjects 2-11 yr (87 subjects 2-6 yr) 128 controls	Loperamide 0.14-0.28 mg/kg/day	Shorter time to last unformed stool (p=0.0017) Median time 26.8 h to 18.5 h Higher rating of efficacy & acceptability. Adverse events in 15% Loperamide group, 7% in placebo p=0.048 e.g. vomiting, nausea, fever, somnolence.
(PPPSG, 2000)[96]	Retrospective questionnaire survey	26 paediatricians	25/26 used loperamide for gastroenteritis in patients above 3 months old. 72% found it "usually useful" and 28% "sometimes useful" in reducing diarrhoea. A dose of 0.1 mg/kg or less given 2-4 times daily [0.2-0.4 mg/kg/day] was most commonly employed.	62% of respondents did not encounter side effects with loperamide. Of 20 cases with side effects recalled by the doctors, 14 had abdominal distension or ileus, and 1 had respiratory depression (attributed to gross overdose by mother). No fatality reported.

Table F (2)   Drug therapy: Bismuth subsalicylate

Authors	Study design	n	Treatment	Results/Comments
(Figueroa-Quintanilla et al, 1993)[103]	Randomised placebo-controlled	275 male infants & young children (mean age 13.5m)	Bismuth subsalicylate 100-150 mg/kg/day	Lower stool output, p=0.015 Lower intake of ORS, p=0.013 Shorter duration of hospitalisation, p=0.005. Bismuth & Salicylate blood level well below toxic level.
(Soriano-Brucher et al, 1991)[104]	Double-blind Placebo-controlled	123 children 4-28 months	Bismuth subsalicylate 100 mg/kg/day	Significant decrease in stool freq. & stool wt Decrease in disease duration (6.9 vs. 8.5 days) Decrease IV fluid requirement. Increase clearance of pathogenic *E. Coli* but not rotavirus No side effect. Bismuth & Salicylate level well below toxic level.

Table F (3)   Drug therapy: Smectite and attapulgite

Authors	Study design	n	Treatment	Results/Comments
(Madkour et al, 1993)[100]	Double-blind Placebo-controlled	90 boys (3-24 m)	Smectite 1.5 gm in 50 ml water QID x 3 days	Shorter duration of diarrhoea. Fewer stools Amount of liquid stools not significantly reduced. Higher wt gain.
(Vivatvakin et al, 1992)[101]	Randomised placebo-controlled	62 children (1-24 m)	Smectite 3.6 gm/day	Shorter duration of diarrhoea (8.4 vs. 4.3 days), p=0.005. Stool frequency and weight changes no significant differences. No side effects.
(Gilbert et al, 1991)[99]		56 (2-24 m)	Smectite, Loperamide or placebo	Diarrhoea resolved faster under Smectite than placebo Similar between Smectite & Loperamide. Smectite was well tolerated.
(Charritat et al, 1992)[97]	Placebo-controlled multicentre study	113 children (mean age 28 m)	Attapulgite	1st & 2nd normal formed stools were passed one day earlier in subjects (p=0.01 & 0.002) resumption of normal diet earlier (4.4 vs 5.1 days). Well tolerated.

Table F (4)   Drug therapy: Probiotics

Authors	Study design	n	Treatment	Results/Comments
(Van Niel et al, 2002)[86]	Meta-analysis	9 RCTs with a total of 391 cases and 374 controls	*Lactobacillus*	Duration of diarrhoea reduced by 0.7 days (95% CI: 0.3-1.2 days) and diarrhoea frequency reduced by 1.6 stools on Day 2 of treatment (95% CI: 0.7-2.6 fewer stools).

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