

Diarrhoea and vomiting caused by gastroenteritis

diagnosis, assessment and management
in children younger than 5 years

Clinical Guideline

April 2009

Funded to produce guidelines for the NHS by NICE

Diarrhoea and vomiting caused by gastroenteritis

diagnosis, assessment and management
in children younger than 5 years

National Collaborating Centre for Women's
and Children's Health

Commissioned by the National Institute
for Health and Clinical Excellence

April 2009



RCOG Press

Published by the **RCOG Press** at the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG

www.rcog.org.uk

Registered charity no. 213280

First published 2009

© 2009 National Collaborating Centre for Women's and Children's Health

No part of this publication may be reproduced, stored or transmitted in any form or by any means, without the prior written permission of the publisher or, in the case of reprographic reproduction, in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK [www.cla.co.uk]. Enquiries concerning reproduction outside the terms stated here should be sent to the publisher at the UK address printed on this page.

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant laws and regulations and therefore for general use.

While every effort has been made to ensure the accuracy of the information contained within this publication, the publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check current indications and accuracy by consulting other pharmaceutical literature and following the guidelines laid down by the manufacturers of specific products and the relevant authorities in the country in which they are practising.

ISBN 978-1-906985-14-1

NCC-WCH Editor: Andrew Welsh

Original design: FiSH Books, London

Typesetting: Andrew Welsh

Proofreading: Katharine Timberlake (Reedmace Publishing Ltd)

Index: Jan Ross (Merrall-Ross (Wales) Ltd)

Contents

Guideline Development Group membership and acknowledgements	v
Guideline Development Group	v
Acknowledgements	vi
Stakeholder organisations	vi
Abbreviations	viii
Glossary of terms	ix
1 Scope and methodology	1
1.1 Introduction	1
1.2 Aim of the guideline	3
1.3 Areas within the scope of the guideline	3
1.4 Areas outside the scope of the guideline	4
1.5 For whom is the guideline intended	4
1.6 Who has developed the guideline?	5
1.7 Guideline development methodology	5
1.8 Schedule for updating the guideline	8
2 Summary of recommendations	9
2.1 Key priorities for implementation (key recommendations)	9
2.2 Summary of recommendations	11
2.3 Key priorities for research	17
2.4 Summary of research recommendations	19
2.5 Flow pathway for fluid management	19
3 Diagnosis	21
3.1 Clinical diagnosis	21
3.2 Laboratory investigations in diagnosis	27
4 Assessing dehydration and shock	38
4.1 Clinical assessment	38
4.2 Laboratory investigations for assessing dehydration	48
5 Fluid management	54
5.1 Primary prevention of dehydration	54
5.2 Treating dehydration	55
5.3 Optimal composition and administration of oral fluids	60
5.4 Intravenous fluid therapy (IVT)	66
5.5 Fluid management following rehydration	74
6 Nutritional management	76
6.1 Feeding during rehydration	76
6.2 Feeding following rehydration	78
7 Antibiotic therapy	90
7.1 Salmonella	90
7.2 Campylobacter	92
7.3 Yersinia	93
7.4 Shigella	94
7.5 <i>Escherichia coli</i>	95
7.6 Cryptosporidium	95
7.7 Treatment without prior identification of a pathogen	96
7.8 Traveller's diarrhoea	98
7.9 Groups for whom antibiotic treatment may be indicated	99

8	Other therapies	104
8.1	Anti-emetics	104
8.2	Antidiarrhoeal agents	109
8.3	Micronutrients and fibre	117
8.4	Alternative and complementary therapies	125
8.5	Probiotics	126
9	Escalation of care	134
10	Information and advice for parents and carers	137
10.1	Caring for a child with diarrhoea and vomiting at home	137
10.2	Preventing primary spread of diarrhoea and vomiting	138
Appendix A	Cost-effectiveness of IVT versus ORT for children with dehydration	140
Appendix B	Health economics of ondansetron	153
	References	157
	Index	163
	Search strategies	NICE website
	Evidence tables	NICE website

Guideline Development Group membership and acknowledgements

Guideline Development Group

GDG members

Stephen Murphy	GDG Chair, Senior Lecturer in Paediatrics and Child Health, Consultant Paediatric Gastroenterologist
Ed Abrahamson	Consultant in Paediatric Emergency Medicine
Richard Churchill	General Practitioner and Clinical Associate Professor
Dianne Cook	Children's Community Specialist Practitioner
John Crimmins	General Practitioner
Saul Faust	Senior Lecturer in Paediatric Infectious Diseases/ Immunology
Alastair Hay	General Practitioner
Naryndar Johal	Parent/carer member
Julie Marriott	Parent/carer member
Nigel Meadows	Consultant Paediatric Gastroenterologist
Simon Minford	Advanced Paediatric Nurse Practitioner
Robert Moy	Senior Lecturer in Community Child Health
Enid Povey	National Clinical Development Manager, NHS Direct
Gyanranjan Prasad Sinha	Consultant Paediatrician
Jenny Taylor	Advanced Paediatric Nurse Practitioner

National Collaborating Centre for Women's and Children's Health (NCC-WCH) staff

Monica Lakhanpaul	Clinical Co-Director, NCC-WCH and Senior Lecturer, Child Health
Rajesh Khanna	Senior Research Fellow
Shona Burman-Roy	Research Fellow
Ana Palanca	Research Fellow
Paul Jacklin	Senior Health Economist
Itrat Iqbal	Health Economist
Danielle Worster	Information Scientist
Rosie Crossley	Work Programme Coordinator
Angela Kraut	Research Fellow
Sjokvist Garcia-Stewart	Research Fellow
Alyson Huntley	Freelance Researcher

External advisers

Craig Williams	Consultant Microbiologist
Martin Richardson	Consultant Paediatrician

Peer reviewer

Olivier Fontaine	Medical Officer, Child and Adolescent Health and Development, World Health Organization
------------------	---

Acknowledgements

Additional support was received from:

- Eva Gautam-Aitken, Anna Bancsi, Martin Dougherty, Wendy Riches, Rupert Franklin and Chris Kitchen at the NCC-WCH
- Caroline Keir at the National Institute for Health and Clinical Excellence (NICE)
- The Patient and Public Involvement Programme (PIIP) for NICE.

Stakeholder organisations

Abbott Laboratories Limited
Association for Continence Advice
Association of Medical Microbiologists
Association of Psychoanalytic Psychotherapy in the NHS
Association of the British Pharmaceuticals Industry (ABPI)
Barnsley Hospital NHS Foundation Trust
Barnsley PCT
Bedfordshire PCT
Berkshire Healthcare NHS Trust
Boehringer Ingelheim Ltd
Bolton Council
Bournemouth and Poole PCT
Bradford & Airedale PCT
Breastfeeding Network, The
British Dietetic Association
British Homeopathic Association
British National Formulary (BNF)
British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN)
Buckinghamshire PCT
Calderdale PCT
Cardiff and Vale NHS Trust
Chelsea & Westminster Acute Trust
CIS'ters
College of Emergency Medicine
Commission for Social Care Inspection
Connecting for Health
ConvaTec
Cornwall & Isles of Scilly PCT
Department for Communities and Local Government
Department of Health
Department of Health, Social Security and Public Safety of Northern Ireland
Derbyshire Mental Health Services NHS Trust
General Chiropractic Council
General Osteopathic Council
GlaxoSmithKline UK
Good Hope Hospitals NHS Trust
Greater Manchester West Mental Health NHS Foundation Trust
Harrogate and District NHS Foundation Trust
Health and Safety Executive
Health Protection Agency
Healthcare Commission
Home Office
Infection Prevention Society
Institute of Biomedical Science
La Leche League GB
Leeds PCT
Liverpool PCT
Luton and Dunstable Hospital NHS Trust

Meat & Livestock Commission
Medicines and Healthcare products Regulatory Agency (MHRA)
Medicines for Children Research Network (MCRN)
Mental Health Act Commission
Milton Keynes PCT
National Childbirth Trust
National Patient Safety Agency (NPSA)
National Pharmacy Association
National Public Health Service – Wales
National Treatment Agency for Substance Misuse
National Coordinating Centre for Health Technology Assessment (NCCHTA)
Neonatal & Paediatric Pharmacists Group (NPPG)
Newham University Hospital NHS Trust
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Kirklees
NHS Plus
NHS Purchasing & Supply Agency
NHS Quality Improvement Scotland
Norgine
North Yorkshire and York PCT
Northwick Park and St Mark's Hospitals NHS Trust
Nottingham University Hospitals NHS Trust
Phoenix Partnership
PERIGON Healthcare
Queen's Medical Centre Nottingham University Hospitals NHS Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Radiologists
Royal Liverpool Children's NHS Trust
Royal Society of Medicine
SACAR
Sandwell PCT
Sanofi-Aventis
Sanofi Pasteur MSD
Scottish Intercollegiate Guidelines Network (SIGN)
Scottish Nutrition & Diet Resources Initiative
Sedgefield PCT
Sefton PCT
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
South Central Ambulance Service NHS Trust
Staffordshire Ambulance HQ
University College London Hospitals (UCLH) Acute Trust
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Western Cheshire PCT
Western Health and Social Care Trust
Wiltshire PCT
Wirral Hospital Acute Trust
York NHS Foundation Trust

Abbreviations

AROC	area under receiver operating characteristic [curve]
BSS	bismuth subsalicylate
BUN	blood urea nitrogen
<i>C. difficile</i>	<i>Clostridium difficile</i>
CI	confidence interval
CRP	C-reactive protein
CRT	capillary refill time
DCRT	digital capillary refill time
<i>E. coli</i>	<i>Escherichia coli</i>
EL	evidence level (level of evidence)
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GDG	Guideline Development Group
HPA	Health Protection Agency
HUS	haemolytic uraemic syndrome
IM	intramuscular
iu	international unit
IV	intravenous
IVT	intravenous fluid therapy
LR	likelihood ratio
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPSA	National Patient Safety Agency
OR	odds ratio
ORS	oral rehydration salt
ORT	oral rehydration therapy
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomised controlled trial
RIV	rapid intravenous hydration
RNG	rapid nasogastric hydration
ROC	receiver operating characteristic
RR	relative risk
SD	standard deviation
SMD	standardised mean difference
UK	United Kingdom
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization
WMD	weighted mean difference

Glossary of terms

Absolute risk or risk	The probability of a disease or an event/outcome occurring (e.g. an adverse reaction to the drug being tested) in a group of people without the disease or event/outcome during a specified time period. Risk and <i>rate</i> are two different measures of incidence , but the distinction between them is relatively recent and many old studies have used the two words interchangeably. Studies that compare two or more groups of patients may report results in terms of the relative risk .
Acidosis	A term used to describe processes tending to lead to a blood pH less than 7.36. When the pH is less than 7.36, this is referred to as acidemia. Clinicians sometimes use the terms acidemia and acidosis interchangeably.
Acute gastroenteritis	See gastroenteritis .
Acute-phase proteins	Blood markers of an inflammatory response
Anthropometric measures	Measurements of the human body or its parts to enable comparisons between individuals of different ages, sexes and races to be made, to determine the difference between normal and abnormal development.
Antidiarrhoeal	A drug that provides symptomatic relief from diarrhoea. These include adsorbent agents (e.g. kaolin, smectite and activated charcoal), bismuth salicylate, antisecretory agents (e.g. racecadotril) and antimotility agents (e.g. loperamide).
Anti-emetic	A drug that relieves nausea and prevents vomiting.
Antimotility agent	A drug that slows the transit of gastrointestinal contents.
Antisecretory agent	A drug that reduces or suppresses intestinal fluid secretion.
Appendicitis	Inflammation of the appendix.
Appraisal of evidence	Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.
Area under ROC curve (AROC)	See receiver operating characteristic curve (ROC curve) .
Association	Relationship between two characteristics that helps to predict change in one when there is a change in the other. The association can be positive (both characteristics change in the same direction) or negative (the characteristics change in the opposite direction).
Best available evidence	The strongest research evidence available to support a particular guideline recommendation.
Bias	Influences on a study that can lead to invalid conclusions about the study results. Also known as systematic error or deviation from truth. It occurs as a result of defects in the study design or the way the study is carried out or owing to confounding variables . Bias can occur at various stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data.
Blinding or masking	The process of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of blinding or masking is to protect against bias . See also double-blind study , single-blind study , triple-blind study .
Bolus fluids	A volume of fluid given quickly.
Capillary refill time (CRT)	A test performed on physical examination in which the skin is pressed by the clinician's finger until blanched and the time taken for the skin to return to its previous colour is measured. Capillary refill time (CRT) can be measured peripherally (in the extremities) or centrally (on the chest wall). A prolonged CRT may be a sign of shock.

Case-control study	A type of observational study that compares a group of individuals with a particular disease or outcome (known as cases) with a group of individuals without the disease or outcome (known as controls). All subjects are then assessed with respect to things that happened to them in the past to explore the association between the disease/outcome and prior exposure to specific risk factors.
Case report (or case study)	A type of observational study with detailed reports on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	A type of observational study with descriptions of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Checklist	See study checklist .
Clinical audit	A systematic process for setting and monitoring standards of clinical care. Whereas ' guidelines ' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy .
Clinical importance	The importance of a particular guideline recommendation to the clinical management of the target population.
Clinical question	A term sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a focused question .
Clinical trial	A research study conducted to compare the effects of two or more healthcare interventions, for example a trial conducted to assess the effectiveness and safety of a new cancer drug compared with the old treatment. Each trial is designed to answer scientific questions and find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials .
Clinician	A healthcare professional providing patient care, for example doctor, nurse, physiotherapist.
Cluster	A group of patients, rather than an individual, used as the basic unit for investigation. They might be families, schools, medical practices or whole communities. See also cluster randomised trial .
Cluster randomised trial	A trial in which groups of individuals or clusters (e.g. patients in a GP surgery or people living in a community) are randomly allocated to treatment groups. It is usually carried out to evaluate the effectiveness of an intervention provided at the community level. Take, for example, a smoking cessation study of two different interventions – leaflets and teaching sessions. Each GP surgery within the study would be randomly allocated to administer one of the two interventions. See also cluster .
Cochrane Collaboration	An international, non-profit, independent organisation that maintains up-to-date information about healthcare interventions by producing and disseminating systematic reviews of their effectiveness. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the Cochrane Library .
Cochrane Library	A regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). The Cochrane Library is available on CD-ROM and the internet.

Coeliac disease	A condition in which the small intestine absorptive surface is damaged owing to an intolerance to gluten. It may lead to impaired digestion and absorption of foods and may be associated with diarrhoea.
Cohort	A group of people sharing some common characteristic or exposure (e.g. people working in a specific environment or patients with the same disease) within a specified period of time.
Cohort study	A type of observational study that takes a group (cohort) of people and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the type of exposure (treatments or interventions) that they received. For example, comparing mortality between one group of patients that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or ' prospective ' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or ' retrospective ' cohort study).
Colloid fluids	Substances that do not dissolve into a true solution and do not pass through a semi-permeable membrane. Colloid solutions tend to remain in the intravascular compartment (within the circulation) longer than crystalloid solutions, and so a smaller amount may be needed to maintain an adequate intravascular volume. Colloids also increase colloidal osmotic pressure, and so draw water from the interstitial spaces into the intravascular compartment. However, when capillary permeability is increased, colloids may leak across the capillary membrane and increase interstitial oncotic pressure, causing oedema. This may also happen if too much colloid is given. Types of colloids include dextran and gelatin (e.g. Gelofusine® and Haemaccel®).
Confidence interval (CI)	A statistical technique used to express uncertainty about the findings from a study or group of studies. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Concealment of allocation or allocation concealment	The process of ensuring that the researcher entering new participants in a randomised controlled trial is unaware of the group (intervention or control) the participants have been allocated/assigned to. This is distinct from blinding and is done to prevent selection bias.
Confounder or confounding factor/variable	A factor or a variable that can distort the true relationship between the exposure/risk factor and outcome in a study and can contribute to misleading findings if it is not understood or appropriately dealt with. It is an important cause of bias in study results and can be dealt with during the stage of study design or data analysis or both. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Consensus methods	A variety of techniques that aim to reach an agreement on a particular issue. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.
Constipation	A condition in which passing faeces occurs infrequently, or with difficulty.
Control group	In a controlled trial it refers to a group of participants recruited to act as a comparator for one or more healthcare intervention. This group may receive no healthcare intervention, continue standard treatment or receive a placebo (dummy treatment) in order to provide a comparison for a group receiving an experimental intervention, such as a new drug. It is also known as a comparison group.

Controlled clinical trial (CCT)	A clinical trial testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial .
Cost–benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-effectiveness	Value for money. A specific healthcare treatment is said to be ‘cost-effective’ if it gives a greater health gain than could be achieved by using the resources in other ways.
Cost-effectiveness analysis	A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in ‘health-related units’, for example, the cost of preventing one additional heart attack.
Cost–utility analysis	A special form of cost-effectiveness analysis where health effects are measured in quality-adjusted life years (QALYs) . A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.
Crohn’s disease	A form of chronic inflammatory bowel disease.
Cross-sectional study	A type of observational study where information is collected from a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study , which follows the same set of people over a period of time.)
Crystalloid fluids	Substances that form a true solution and pass freely through a semi-permeable membrane. They contain water and electrolytes and stay in the intravascular compartment for a shorter time than colloids. Around 2–3 times more crystalloid than colloid is needed to achieve an equivalent haemodynamic response. Crystalloids are useful in maintaining fluid balance. The type of crystalloid given as fluid maintenance needs to be tailored to the need of the patient and has to take into account the daily requirement, insensible losses and measured losses of fluid and electrolytes. Types of crystalloid include normal saline, dextrose 5% and Hartmann’s solution (sodium lactate).
Cytotoxin	A drug that damages or destroys cells.
Decision analysis	Decision analysis is the study of how people make decisions or how they should make decisions. There are several methods that decision analysts use to help people to make better decisions, including decision trees .
Decision tree	A decision tree is a method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or overall cost-effectiveness of different actions can then be compared.
Declaration of interest	A process by which members of a working group or committee ‘declare’ any personal or professional involvement with a company (or related to a technology) that might affect their objectivity, for example if their position or department is funded by a pharmaceutical company.
Dehydration	A state arising from loss of extracellular fluids and/or intracellular fluid.
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease, rather than to assess patient-related outcomes. The accuracy of the test is compared with some method (which is also known as the reference standard) of determining the true disease status.
Dominance	A term used in health economics describing when an option for treatment is both less clinically effective and more costly than an alternative option. The less effective and more costly option is said to be ‘dominated’.

Double-blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias .
Dysentery	An infection of the intestinal tract that causes diarrhoea with blood and mucus.
Dysuria	Pain on passing urine.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In health economic evaluations, the consequences should include health outcomes.
Effectiveness	See clinical effectiveness .
Efficacy	The extent to which a specific treatment or intervention has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care under controlled clinical conditions, for example in a laboratory.
Elective	Clinical procedures that are regarded as advantageous to the patient but not urgent.
Endemic	Diseases that are present in or peculiar to particular localities or populations.
Enteric infection	Infection of the intestine.
Epidemiology	The study of diseases within a population, covering the causes and means of prevention.
Erythrocyte sedimentation rate (ESR)	A measure of the settling of red blood cells in a tube of blood during 1 hour. The rate is an indication of inflammation and increases in many diseases.
Evidence-based clinical practice	Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.
Evidence level	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles. Also called level of evidence .
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria	See selection criteria .
Experimental study	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease, where the conditions of testing are to some extent under the control of the investigator. Also known as an intervention study . Controlled clinical trials and randomised controlled trials are examples of experimental studies.
Experimental treatment	A treatment or intervention (e.g. a new drug) being studied to see whether it has an effect on the course or outcome of a condition or disease.
External validity	The degree to which the results of a study hold true in non-study situations, for example in routine clinical practice. May also be referred to as the generalisability or applicability of study results to non-study patients or populations.
Focused question	A study question that clearly identifies all aspects of the topic that are to be considered while seeking an answer. Questions are normally expected to identify the patients or population involved, the treatment or intervention to be investigated, what outcomes are to be considered, and any comparisons that are to be made. For example, do insulin pumps (intervention) improve blood sugar control (outcome) in adolescents with type 1 diabetes (population) compared with multiple insulin injections (comparison)? See also clinical question .
Forest plot	A graphical display of results from individual studies included in a meta-analysis together with the pooled meta-analysis result. This allows visual comparison of results from individual studies and examination of the degree of heterogeneity between studies.

Gastroenteritis	A transient disorder due to enteric infection and characterised by the sudden onset of diarrhoea with or without vomiting.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also external validity .
Gold standard	A method, procedure or measurement that is widely accepted as being the best available, against which new developments should be compared.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in easily accessible bibliographic retrieval system (such as journals or databases).
Guideline	A systematically developed tool that describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available rather than on opinion. It is used to assist clinician and patient decision making about appropriate health care for specific clinical conditions.
Guideline recommendation	Course of action advised by the Guideline Development Group on the basis of their assessment of the supporting evidence.
Health economics	A branch of economics that studies decisions about the use and distribution of healthcare resources.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.
Health Technology Appraisal (HTA)	The process of determining the clinical and cost-effectiveness of a health technology undertaken by NICE to provide patients, healthcare professionals and managers with an authoritative source of advice on new and existing health technologies.
Hepatosplenomegaly	Abnormal enlargement of both the liver and the spleen.
Heterogeneity	In the general sense, the term is used to describe variation in the participants, interventions and outcomes across a set of studies. Statistical heterogeneity is the term used in meta-analyses and systematic reviews to describe variation in the results or estimates of effects beyond the amount expected solely due to chance. It is the opposite of homogeneity .
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions drawn from a well-conducted study. A systematic review of good-quality randomised controlled trials (RCTs) with homogeneity in their results (which are statistically significant) is at the top of this hierarchy. Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	In the general sense, the term is used to imply similarity in the participants, interventions and outcomes across a set of studies. Statistical homogeneity means that the results of studies or estimates of effects included in a systematic review or meta-analysis are similar or they do not vary beyond the amount expected by chance. It is the opposite of heterogeneity .
Hyperchloraemic acidosis	An electrolyte and acid/base disturbance that may arise as a consequence of infusing large quantities of chloride-containing solutions, such as 0.9% normal saline.
Hyperglycaemia	An abnormally high level of glucose in the bloodstream.
Hyperkalaemia	An electrolyte disturbance in which the plasma potassium concentration is greater than 5.5 mmol/l.
Hypernatraemia	An electrolyte disturbance in which the plasma sodium concentration is greater than 145 mmol/l. In severe hypernatraemia (e.g. plasma sodium levels more than 160 mmol/l), there are risks associated with a sudden fall in plasma sodium level during rehydration, and such patients require a modified approach to their fluid management.
Hyperreflexia	Overactive or overresponsive reflexes.
Hypertonicity	Abnormally high muscle tension.
Hypoglycaemia	An abnormally low level of glucose in the bloodstream.

Hyponatraemia	An electrolyte disturbance in which the plasma sodium concentration is less than 135 mmol/l.
Hypovolaemic shock	A state of decreased blood volume or more specifically of blood plasma volume that results in inadequate circulation of blood to the body tissues.
<i>P</i>	A quantitative measure of statistical heterogeneity which describes the percentage of variability in the study results or effects of estimates that is beyond the amount expected by chance. Generally, a value greater than 50% is considered to represent substantial heterogeneity.
Immunocompromised	A congenital or acquired condition in which the immune system is functionally impaired, resulting in an increased risk of infection.
Incidence	Incidence and prevalence are tools to describe how common a disease or an event/outcome is with reference to the size of population. Incidence measures the frequency of disease or an event/outcome in new cases only. The two commonly used measures of incidence are the risk or absolute risk and the rate.
Inclusion criteria	See selection criteria .
In-depth interview	A qualitative research technique. It is a face-to-face conversation between a researcher and a respondent with the purpose of exploring issues or topics in detail. It does not use pre-set questions, but is shaped by a defined set of topics or issues.
Infant	A child younger than 1 year.
Inflammatory bowel disease	A group of chronic intestinal diseases characterised by inflammation of the gastrointestinal tract. The two most common types of inflammatory bowel disease are Crohn's disease and ulcerative colitis.
Intention-to-treat analysis	A strategy used in randomised controlled trials whereby data from study participants are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of clinical effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.
Internal validity	Refers to the integrity of the study design or the extent to which the study design was successful in preventing bias . See also methodological quality .
Intervention	Healthcare action intended to benefit the patient, for example drug treatment, surgical procedure, psychological therapy, etc.
Intervention or experimental group	A group of participants in a study who receive a specific healthcare intervention. See also control group .
Intestinal obstruction	A blockage of the intestine typically resulting in symptoms such as abdominal pain and vomiting.
Intravenous fluid therapy (IVT)	The administration of fluids directly into the venous circulation.
Intussusception	A condition in which a part of the intestine prolapses (telescopes) into another immediately adjacent section of the intestine, typically resulting in symptoms of intestinal obstruction . It can lead to gangrene of the affected gut segment.
Kwashiorkor	A state of severe protein malnutrition marked by lethargy, growth restriction, anaemia, oedema, potbelly, skin depigmentation, and hair loss or change in hair colour.
Level of evidence	See evidence level .
Leucocytosis	An abnormally high level of white cells (leucocytes) in the blood.
Likert scale	A survey method of measuring attitudes that asks respondents to specify their level of agreement with a statement.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
Longitudinal study	A type of observational study that follows a group of people at more than one point in time or where repeated observations are made. (This type of study contrasts with a cross-sectional study , which observes a defined set of people at a single point in time.)

Malabsorption	The reduced absorption of one or more substances by the small intestine.
Masking	See blinding .
Matching	A method to minimise bias in a case-control study whereby people in the control group are selected if they have particular attributes (e.g. age, sex) similar to those of the individual cases.
Mean or arithmetic mean	Also known as the average value, it is calculated by dividing the sum of all the observations by the number of observations.
Mean difference or weighted mean difference (WMD)	A method used in meta-analysis to combine (or pool) the outcomes measured in a continuous scale (e.g. weight, age). The results of each study included in the meta-analysis are given a weight depending on the influence it has on the overall pooled results or the precision of its effect estimate. This is different from the standardised mean difference (SMD) .
Meta-analysis	A statistical technique used in a systematic review to combine (pool) the results from a collection of independent studies into a single estimate of a treatment effect. Where studies are not compatible, for example because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also systematic review and heterogeneity .
Methodology	The overall approach of a research project, for example the study will be a randomised controlled trial, of 200 people, over 1 year.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods. Also known as study quality . See also internal validity .
Mucoprotective agent	A therapeutic agent that protects the lining (mucosa) of the gut.
Multicentre study	A study where subjects are selected from different geographical locations or sites, for example a cooperative study between different hospitals or an international collaboration involving patients from more than one country.
National Patient Safety Agency (NPSA)	Leads and contributes to improved, safe patient care by informing, supporting and influencing the health sector.
Negative likelihood ratio (-LR)	A measure used to give an informative value of a test result and which is calculated as the ratio between $1 - \text{sensitivity}$ and specificity . It is used to describe how much to decrease the probability of a disease if the test is negative (or rule out a disease). The lower the negative likelihood ratio (less than 1) for a test result, the less the likelihood of the disease.
Negative predictive value	In diagnostic testing, this expresses the probability that someone with a negative test result does not have the condition of interest.
NHS Direct	A service that provides 24 hour confidential health advice and information. NHS Direct can help people who are feeling ill, are unsure what to do, would like to find out more about a condition or treatment, or need details of local health services. The service can be accessed by visiting www.nhsdirect.nhs.uk , going to NHS Direct Interactive on digital satellite TV (by pressing the interactive button on the remote control) or by calling 0845 4647.
NNH	Number needed to harm. See number needed to treat .
NNT	See number needed to treat .
Non-experimental study	See observational study .
Number needed to treat (NNT)	This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order for one patient to get a beneficial outcome or prevent an adverse outcome. For example, if the NNT = 4, then four patients would have to be treated to prevent one bad outcome. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the number needed to harm (NNH), which is the number of patients that would need to receive a treatment to cause one additional adverse event. For example, if the NNH = 4, then four patients would have to be treated for one bad outcome to occur.
Objective measure	A physical or biological measurement that follows a standardised procedure and is less open to subjective interpretation by potentially biased observers and study participants.

Observational study	In research, this refers to a study in which nature is allowed to take its course and the investigator simply observes what is happening. Also known as a non-experimental study . Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies . There are various types of observational studies, such as cohort study , case-control study , cross-sectional study and case series .
Odds	Odds are a way of representing probability, especially familiar for betting. It is calculated by dividing the number of people with a defined outcome or event in a given sample of population with the number of people who did not have that outcome or event.
Odds ratio (OR)	The ratio of the odds of an outcome in one group of people to the odds in another group of people. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. An odds ratio of 1 between two treatment groups for a specific outcome would imply that the risk of that outcome is the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also relative risk or risk ratio (RR) .
Oral rehydration salt (ORS) solution	Specially constituted fluid containing as essential ingredients an organic solute (e.g. a carbohydrate or amino acid) and sodium chloride. Such organic solutes are subject to active intestinal co-transport (absorption) with sodium and so enhance salt and hence water absorption. Most ORS solutions contain glucose as the organic solute.
Oral rehydration therapy (ORT)	The administration of fluids by mouth or via nasogastric tube.
Osmolarity	Osmotic concentration.
Osmosis	The movement of solvent molecules across a membrane to an area where there is a higher concentration of solute to which the membrane is impermeable.
Outcome	The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.
Paralytic ileus	A functional obstruction of the ileum (bowel) due to loss of intestinal movement.
Parasite	An organism that obtains food and shelter from another organism.
PCT	See primary care trust .
Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional and/or patient/carer representatives.
Phlebitis	Inflammation of a vein.
Photophobia	An abnormal intolerance to light.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial and which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
Point estimate	The best single estimate for the true value of a treatment effect or other measurement obtained from a research study. For example, researchers in one clinical trial take their results as their best estimate of the real treatment effect for the population from which the study sample was selected – this is their estimate at their point in time. The precision or accuracy of the estimate is measured by a confidence interval .

Positive likelihood ratio (+LR)	A measure used to give an informative value of a test result and which is calculated as the ratio between sensitivity and $1 - \text{specificity}$. It is used to describe how much to increase the probability of a disease if the test is positive (or rule in a disease). The higher the positive likelihood ratio (more than 1) for a test result, the greater the likelihood of the disease.
Positive predictive value	In diagnostic testing, this expresses the probability that someone with a positive test result does have the condition of interest.
Power	See statistical power .
Prevalence	Prevalence and incidence are tools to describe how common a disease or an event/outcome is with reference to the size of population. Prevalence is the proportion of people in a defined population that have the disease or an event/outcome at a specific time. In contrast to incidence , which quantifies disease frequency among new cases only, prevalence measures disease frequency in both old and new cases (all existing cases) at a particular time.
Primary care	Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary care trust (PCT)	An NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called primary care) and making sure that other appropriate health services are in place to meet local people's needs.
Primary outcome	An outcome deemed <i>a priori</i> to be of greatest importance at the start of a research study.
Probability	How likely an event is to occur, for example how likely a treatment or intervention will alleviate a symptom.
Probiotic	A live microbial food which is intended to have beneficial effects by improving the intestinal microbial balance of the host.
Prognostic factor	Patient or disease characteristics, for example age or comorbidity, that influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in variables (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis, these prognostic factors become confounding factors .
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective .
Protocol	A plan or set of steps that defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.
P value	If a study is done to compare two treatments then the <i>P</i> value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the <i>P</i> value was $P = 0.03$. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of <i>P</i> is below 0.05 (i.e. less than 5%) the result is considered to be statistically significant.
Pyloric stenosis	Narrowing of the stomach outlet so that food cannot pass easily from it into the intestine. This condition is usually seen in young infants, and is associated with persistent vomiting.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, for example a patient's description of their pain rather than a measure

	of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quality-adjusted life years (QALYs)	A measure of health outcome which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0 to 1 scale). 1 QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census that counts people and households.
Quasi-random allocation	A method of assigning or allocating participants in an experimental study whereby the assignment of patients to treatment and comparison groups is not done randomly, or patients are not given equal probabilities of selection. For example, participants may be assigned to the groups based on their date of birth or day of the week or every alternate person. These methods lead to selection bias in a study. See also random allocation .
Random allocation	A method that uses the play of chance to assign participants or units to comparison groups in an experimental study , for example by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions. See also quasi-random allocation .
Randomisation	The process of randomly allocating participants into comparison groups in a controlled trial. The aim of this process is to ensure that the experimental and the control groups are similar with respect to all potential confounding variables except the treatment or intervention being investigated.
Randomised controlled trial (RCT)	An experimental study to test a specific drug or other treatment in which people are randomly allocated to two (or more) groups: one (the intervention or experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was.
Receiver operating characteristic curve (ROC curve)	A curve representing the relationship between sensitivity (true positive fraction and $1 - \text{specificity}$ (false positive fraction) in the case of a continuous test result. It displays the trade-offs between sensitivity and specificity when the cut-off value for a positive test result is varied. The measure used to determine the overall accuracy of a test using the ROC curve is known as the area under ROC curve (AROC) . In general, an AROC of 0.5–0.7 is associated with a marginally useful test, of 0.7–0.9 with a good test, and of greater than 0.9 with an excellent test.
Red flag symptoms and signs	Important symptoms or signs of dehydration whose presence is associated with a risk of progression to shock.
Remote assessment	An assessment carried out when the patient is geographically remote from the assessor (e.g. via telephone) such that physical examination is not possible.
Regression analysis	A statistical technique used to predict the effect or influence of one or more independent factors/ variables on a dependent factor/ variable , for example the effect of age, smoking and occupation on the incidence of lung cancer. Logistic regression and meta-regression are two types of regression analysis.
Relative risk or risk ratio (RR)	The ratio of the risks of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups, the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment.

Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession, and if their assessments tend to agree then the method of assessment is said to be reliable.
Retrospective study	A retrospective study deals with events or outcomes that have already occurred in the past and does not involve studying future events. This contrasts with studies that are prospective .
Risk	See absolute risk or risk .
Risk difference (RD)	The absolute difference between the risks of two groups. Also known as absolute risk difference .
Royal Colleges	In the UK medical/nursing world the term 'royal colleges', as for example in 'The Royal College of ...', refers to organisations that usually combine an educational standards and examination role with the promotion of professional standards.
Safety netting	The provision of support for patients in whom the clinician has some uncertainty as to whether the patient has a self-limiting illness and is concerned that their condition may deteriorate. Safety netting may take a number of forms, such as dialogue with the patient or carer about symptoms and signs to watch for, advice about when to seek further medical attention, review after a set period, and liaising with other healthcare services.
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN was established in 1993 to sponsor and support the development of evidence-based clinical guidelines for the NHS in Scotland.
Secondary care	Care provided in hospitals.
Secondary outcome	An outcome deemed <i>a priori</i> as less important than the primary outcome and is measured to evaluate additional effects of the intervention.
Selection bias	A type of bias that occurs if: <ul style="list-style-type: none">• the characteristics of the sample differ from those of the wider population from which the sample has been drawn, or• there are systematic differences between comparison groups in a study in terms of prognosis or responsiveness to treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Semi-structured interview	Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
Sensitivity	In diagnostic testing, this refers to the proportion of cases with the target condition correctly identified by the diagnostic test out of all the cases that have the target condition.
Shock	A pathological condition in which there is inadequate blood perfusion of the vital organs.
Single-blind study	A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.
Skin turgor	A term used to describe a physical characteristic of the skin. In patients with clinical dehydration, skin turgor may be reduced, so that when a fold of skin is gently pinched and then released it fails to immediately retract in the normal way, but rather retains a ridged appearance for a variable period owing to a reduction in its fluid content.

Specificity	In diagnostic testing, this refers to the proportion of cases without the target condition correctly identified by the diagnostic test out of all the cases that do not have the target condition.
Standard deviation (SD)	A measure of the spread, scatter or dispersion of a set of measurements. Usually used along with the mean (average) to describe numerical data.
Standardised mean difference (SMD)	The difference in the means divided by a standard deviation. This standard deviation is the pooled standard deviation of participants' outcomes across the whole trial. An important difference from the weighted mean difference (WMD) is that the value of the SMD is not dependent on the measurement scale or unit, for example different trials may be assessing the same outcome (such as weight) but using different scales/units for measuring it (such as kilograms or ounces).
Statistical power or power	The ability of a study to demonstrate a statistically significant result (association or difference between two variables) given that such a result exists in the population from which the sample was recruited. For example, 80% power in a clinical trial means that the study has an 80% chance of ending up with a <i>P</i> value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also <i>P</i> value .
Structured interview	A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.
Study checklist	A list of questions addressing the key aspects of the research methodology that must be in place if a study is to be accepted as valid. A different checklist is required for each study type. These checklists are used to ensure a degree of consistency in the way that studies are evaluated.
Study population	People who have been identified as the subjects of a study.
Study quality	See methodological quality .
Study type	The kind of design used for a study. Randomised controlled trial , case-control study and cohort study are all examples of study types.
Subject	A person who takes part in an experiment or research study.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic error	See bias .
Systematic review	A study with a clearly formulated question that uses systematic and explicit methods with predetermined criteria to identify, appraise and synthesise the results of relevant research. It may or may not include a meta-analysis to summarise the results.
Systemic	Involving the whole body.
Tachycardia	An abnormally rapid heart rate.
Tachypnoea	An abnormally rapid breathing rate.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study, for example in terms of age, disease state or social background.
Tertiary centre	A major medical centre providing complex treatments that receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also primary care and secondary care .
Toxic shock syndrome	A state of acute shock, due to septicaemia, that can be life-threatening if not treated.
Triple-blind study	A study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and investigators/clinicians being unaware which treatment patients were getting.

Trust	A trust is an NHS organisation responsible for providing a group of healthcare services. An acute trust provides hospital services. A mental health trust provides most mental health services. A primary care trust buys hospital care on behalf of the local population, as well as being responsible for the provision of community health services.
Ulcerative colitis	A type of inflammatory bowel disease affecting the large intestine (colon).
Validity	An assessment of how well a tool or instrument measures what it is intended to measure. See also external validity and internal validity .
Variable	A factor that differs among and between groups of people. It includes participant characteristics (such as age or sex) or measurements (such as blood pressure or heart rate) or treatments (such as drugs).
Weighted mean difference (WMD)	See mean difference or weighted mean difference (WMD) .

1 Scope and methodology

1.1 Introduction

When young children suddenly experience the onset of diarrhoea, with or without vomiting, infective gastroenteritis is by far the most common explanation. A range of enteric viruses, bacteria and protozoal pathogens may be responsible. Viral infections account for most cases in the developed world. Gastroenteritis is very common, with many infants and young children experiencing more than one episode in a year.

The symptoms of gastroenteritis are unpleasant and the illness has an impact on both child and family. Vomiting causes distress and anxiety. Diarrhoea is often accompanied by abdominal pain. Infants and young children with severe symptoms may quickly become dehydrated. Dehydration is a serious and potentially life-threatening condition.

The management of young children with gastroenteritis involves many considerations. Depending on the specific circumstances, care may be provided by parents or by a range of healthcare professionals. Children may be managed in a community or a hospital setting. There is debate and controversy regarding various aspects of clinical management. Clinical practice may have a major impact on the use of healthcare resources. Finally, there is evidence of considerable variation in practice in the management of children with gastroenteritis in the UK. It was for these reasons that this NICE clinical guideline on the 'management of acute diarrhoea and vomiting due to gastroenteritis in children under 5' was developed.

Gastroenteritis – the global perspective

Viewed from a global perspective, gastroenteritis in children is of enormous public health importance.¹ Worldwide, approximately 1 billion people have no access to safe water and 2.6 billion people lack proper sanitation. About 10.6 million children still die every year before reaching their fifth birthday. Overwhelmingly, these deaths occur in low-income and middle-income countries. A global picture of the important causes of mortality in the young has emerged from collaborative work involving WHO, UNICEF, and a group of independent technical experts – the Child Health Epidemiology Reference Group.² Most deaths among children under 5 years are attributable to a very small number of infectious conditions. Undernutrition increases the risk of death from these disorders. Gastroenteritis alone is responsible for almost 20% of the deaths.

In the 1970s, there were almost 5 million childhood deaths worldwide from gastroenteritis each year. The use of oral rehydration therapy (ORT), arguably the greatest medical discovery of the 20th century, contributed to a marked reduction in this death rate. Nevertheless, gastroenteritis still causes between 1.6 and 2.6 million deaths in children younger than 5 years each year.³

Efforts at further reducing the death rate continue, with strategies focusing on prevention, nutrition and improved fluid management. Other interventions of major importance include the administration of zinc supplements⁴ and the use of antibiotic therapy for dysentery.

Gastroenteritis in the developed world

Deaths associated with gastroenteritis are now quite rare in developed countries. Nevertheless, gastroenteritis remains a potentially serious illness for the individuals affected and it poses a major burden for health services.

In the USA in the 1990s, it was estimated that childhood diarrhoea was responsible for 200 000 hospitalisations and 300 deaths in children younger than 5 years each year, and had an economic cost of \$2 billion.⁵ Recently, a prospective observational study was undertaken in selected areas of Belgium, France, Germany, Italy, Sweden, and the UK to determine the incidence of gastroenteritis and of rotavirus gastroenteritis (the most common responsible pathogen) in

children younger than 5 years who received medical treatment in primary care settings, in hospital emergency departments and as hospital inpatients.⁶ Approximately 10% of children younger than 5 years presented to healthcare services with gastroenteritis each year. Rotavirus infection accounted for 28–52% of cases of gastroenteritis identified in the study. The incidence of rotavirus gastroenteritis was 2.27–4.97 cases per 100 children. In another study looking at cost-of-illness and conducted as part of a community surveillance study, it was estimated that the burden of rotavirus gastroenteritis in the UK amounted to £11.5 million each year.⁷ Recently it was estimated that rotavirus alone was responsible for 60 000 hospitalisations and 37 deaths each year in the USA.⁸ A recent European study also suggested that rotavirus infection was responsible for 72 000–77 000 hospital admissions from among the 23 million children younger than 5 years living in the European Union.⁹ This was associated with an estimated median cost of €1,417 per child. The hospital admission rate for children with gastroenteritis has not declined in recent years, and may have increased.¹⁰

Gastroenteritis in the UK

A study from England provided an estimate of the overall rates of infectious intestinal disease in the community and presenting to primary medical care.¹¹ This involved 70 general practices (primary care medical practices), together serving a population of almost half a million people. Based on prospective reporting, it appeared that about 1 in 5 people experienced symptoms of gastroenteritis each year, but only 1 in 30 presented to their doctor. The authors estimated that in England each year, 9.4 million cases of gastroenteritis occurred in the community and 1.5 million presented to their primary care doctor.

In infants and children, gastroenteritis is often a relatively mild illness lasting only for a few days. Parents often manage their child's illness at home, and in some cases they may not even seek professional advice. However, a very large number of children do present to healthcare professionals for advice. In the UK, parents may contact NHS Direct – a telephone-based service providing remote assessment and advice. Parents may also seek advice from community-based nurses or health visitors or from primary care doctors (general practitioners). Others go directly to a hospital emergency department. In one study from the UK, diarrhoeal illness accounted for 16% of medical presentations to a major paediatric accident and emergency department.¹²

Although most children with gastroenteritis do not require admission to hospital, many are treated as inpatients each year. Once admitted they often remain in the hospital for several days. This is a significant burden for the health services.¹³ Admission also carries a serious risk of spread to other children in the hospital, some of whom may be highly vulnerable as a consequence of their own medical conditions.¹⁴

Developments, controversies and variation in clinical practice

The management of gastroenteritis in children is multifaceted and changing. New treatments and management strategies are being proposed, whose roles may be controversial. New strategies are being evaluated for 'rapid rehydration' with intravenous fluids. Various approaches to the clinical assessment of dehydration severity and hence to the calculation of fluid deficits have been proposed. A variety of new therapies, including anti-emetic and antidiarrhoeal drugs, have been advocated for use in gastroenteritis, but there are uncertainties about the efficacy and safety of these agents. The antisecretory agent racecadotril is not licensed for use in the UK but is used elsewhere in Europe. Recently much interest has been expressed regarding the possible benefits of probiotic preparations in the treatment of gastroenteritis.

Against this changing background, and despite the existence of a number of guidelines, it has long been recognised that there is considerable variation in clinical practice. There is inconsistency in the advice offered to parents regarding the types of oral fluids to be given. Practice still varies in relation to the use of oral versus intravenous fluids for rehydration. Administration of fluids via a nasogastric tube is advocated by some but others avoid this practice. The nutritional management of infants and children during and after the episode of gastroenteritis is often inconsistent. It seems certain that there is variation in the approach to 'escalation of care' from the community to various hospital settings (day wards or inpatient management). A recent population-based study reported significant variation in hospitalisation rates among children with rotavirus gastroenteritis in different European countries.¹⁵

The need for a guideline

A number of recommendation and guidelines on the management of gastroenteritis in childhood have been published.^{16–22} However, this guideline is unique.

Some guidelines have focused on specific subgroups of children, such as those presenting to a hospital setting. This guideline is intended to apply to children younger than 5 years in England and Wales who present to a healthcare professional for advice in any setting. Importantly, it differs from other guidelines in that it was developed using a set of important principles employed for all NICE clinical guidelines. At the outset there was a process of national consultation to determine the key areas of management that should be addressed and to define the exact ‘scope’ of the guideline. Recommendations were based on the best available evidence whenever possible. A systematic and thorough approach was employed to identify relevant research evidence and to evaluate the available studies. For this guideline much of the best evidence is from developing countries and must be interpreted in that light. As there are often important differences in the baseline characteristics of the population, it cannot automatically be assumed that developing country evidence is applicable to a UK setting. For example, malnutrition may often be an important clinical feature of gastroenteritis in developing countries, leading to markedly different outcomes than would be observed in a developed country setting. In interpreting developing country evidence, relative effect measures, especially from large meta-analyses, are generally more stable than absolute measures of effect. Variation in baseline characteristics means that evidence based on absolute measures cannot reliably be applied to a developed country setting. However, even relative measures of effect need to be interpreted with a view as to whether the context is sufficiently similar: ‘Is my patient so different from those in the trial that its results cannot help me make my treatment decision?’²³ This very much reflected the Guideline Development Group (GDG) approach in discussing evidence for this guideline from developing country settings.

The GDG responsible for the guideline recommendations was constituted so as to include individuals with a wide range of relevant personal and clinical expertise. Various authors have commented on the difficulty of implementing guideline recommendations.²⁴ In part this may reflect the practical difficulties of following recommendations in a real setting – taking account of practical impediments and professional or parental perceptions or views. The GDG included parents with personal experience of caring for ill children. It included doctors and nurses working in the community, and in primary, secondary and tertiary healthcare settings. It was supported by a professional ‘technical team’ including information scientists, expert research staff and health economists. External expert advisers were appointed to assist the GDG in its consideration of various complex technical matters. External peer reviewers commented on the guideline during its development. Inevitably, evidence was sometimes limited or non-existent and, in such situations, recommendations were based on GDG consensus opinion. The GDG was able to make recommendations on priority areas for future research. Lastly, there was a process for consultation with ‘stakeholder’ organisations on a draft version of the guideline prior to publication in its final form.

1.2 Aim of the guideline

Clinical guidelines have been defined as ‘systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions’.²⁵ The guideline has been developed with the aim of providing guidance on the diagnosis, assessment and management of children younger than 5 years with acute diarrhoea and vomiting caused by gastroenteritis in England and Wales.

1.3 Areas within the scope of the guideline

Population

- Infants and young children from birth up to their fifth birthday presenting to healthcare professionals with acute diarrhoea (lasting 14 days or fewer) due to gastroenteritis, on its own or with vomiting.

Setting

- Community care, primary care and secondary care, and indications for referral.

Management

- When to consider the management of acute diarrhoea and vomiting in infants and young children who were previously healthy.
- How to identify infants and young children with acute diarrhoea and vomiting who are at risk of dehydration and whose condition needs immediate management.
- How to differentiate between acute infective diarrhoea and diarrhoea due to other causes.
- How to manage symptomatic infants and young children, including:
 - when to start rehydration
 - what type of rehydration fluids to use
 - what route of administration to use
 - what additional treatment to consider
 - appropriate feeding strategies for infants with gastroenteritis
 - when and what investigations should be performed.
- Threshold of referral:
 - what clinical signs or symptoms can be used to identify infants and young children who should be referred
 - what additional factors should be taken into consideration when deciding whether or not to admit an infant or young child to hospital.
- Following the infant or young child's initial assessment by the healthcare professional, what information should be given to parents and carers, for example regarding signs of dehydration, and replacement of fluids and feeding strategies at home.

1.4 Areas outside the scope of the guideline

Population

- Children who have passed their fifth birthday.
- Infants and young children with chronic diarrhoea and vomiting (lasting more than 14 days).
- Infants and young children with disorders other than gastroenteritis that cause diarrhoea or vomiting (for example, specific food intolerances or inflammatory bowel disease).
- Children with medical disorders that significantly alter the approach to their fluid management, such as those with cardiac or renal failure.
- Neonates who are admitted to the neonatal unit.

Management

- Public health issues such as the contamination of food products and factors that may prevent acute diarrhoea and vomiting, for example breastfeeding.
- Immunisations to prevent diarrhoea and vomiting.

1.5 For whom is the guideline intended

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England, Wales and Northern Ireland, in particular:

- general practitioners, paediatricians, gastroenterologists, emergency department physicians, nurses and any healthcare professional involved in the care or management of children younger than 5 years with diarrhoea and vomiting.
- those responsible for commissioning and planning healthcare services, including primary care trust and local health board commissioners, Wales commissioners, and public health and trust managers
- parents/carers and families of children.

A version of this guideline for parents, carers and the public is available, entitled 'Understanding NICE guidance: Diarrhoea and vomiting in children'. It can be downloaded from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/CG84publicinfo).

For printed copies, phone NICE publications on 0845 003 7783 or e-mail publications@nice.org.uk (quote reference number N1845).

1.6 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). The membership included:

- two paediatric gastroenterologists (including the Chair)
- two general paediatricians, one of whom was a community paediatrician
- one paediatric specialist in infectious diseases
- one emergency department paediatric specialist
- three general practitioners
- three nurses, including one emergency nurse practitioner
- one nurse with expertise in remote assessment through a role in NHS Direct
- two patient/parent/carer members.

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval and appraisal of the evidence, health economics modelling and, together with the Chair, wrote successive drafts of the guideline.

All GDG members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry.

1.7 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in the NICE *Technical Manual*.²⁶

1.7.1 Literature search strategy

Initial scoping searches were executed to identify relevant guidelines (local, national and international) produced by other development groups. The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG provided it was relevant to the clinical questions and of equivalent or better quality than evidence identified by the search strategies.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases on the OVID platform: MEDLINE (1950 onwards); Embase (1980 onwards); Cumulative Index to Nursing and Allied Health Literature (1982 onwards); Cochrane Central Register of Controlled Trials (1991 to 3rd quarter 2008); Cochrane Database of Systematic Reviews (3rd quarter 2008); and Database of Abstracts of Reviews of Effects (1991 to 3rd quarter 2008).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were applied to searches – searches were limited to English language papers only. Both generic and specially developed methodological search filters were used appropriately.

Searches to identify economic studies were undertaken using MEDLINE (1950 onwards); Embase (1980 onwards); the Health Technology Assessment database (2nd quarter 2008); and the NHS Economic Evaluations Database (NHS EED, 2nd quarter 2008) produced by the Centre for Reviews and Dissemination (CRD) at the University of York.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

All searches were conducted between 21 September 2007 and 27 May 2008. Searches for clinical questions were rerun from 12 to 14 August 2008, before the start of the consultation period. This date period should be considered the starting point for searching for new evidence for future updates to this guideline.

The detailed search strategies, including the methodological filters employed, are provided on the accompanying CD-ROM, and on the NICE website.

1.7.2 Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides^{26–33} and classified using the established hierarchical system shown in Table 1.1.³³ This system reflects the susceptibility to bias that is inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each study receives a quality rating coded as ‘++’, ‘+’ or ‘–’. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs) (EL = 1++) or an individual RCT (EL = 1+). Studies of poor quality are rated as ‘–’. Usually, studies rated as ‘–’ should not be used as a basis for making a recommendation, but they can be used to inform recommendations. For issues of clinical presentation, the highest possible level of evidence is a cohort study (EL = 2++).

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not included. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought.

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated ranking system for these types of study, NICE has developed a hierarchy for evidence of accuracy of diagnostic tests that takes into account the various factors likely to affect the validity of these studies as seen in Table 1.2.²⁶

For economic evaluations, the search strategies adopted were designed to identify any relevant economic studies. Abstracts of all papers identified were reviewed by the health economists and were discarded if they did not relate to the economic question being considered in the guideline. The relevant papers were retrieved and critically appraised. Potentially relevant references in the bibliographies of the reviewed papers were also identified and reviewed. All papers reviewed were assessed by the health economists against standard quality criteria for economic evaluation.³⁴

Table 1.1 Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

Table 1.2 Levels of evidence for studies of the accuracy of diagnostic tests²⁶

Level	Type of evidence
Ia	Systematic review (with homogeneity) ^a of level-1 studies ^b
Ib	Level-1 studies ^b
II	Level-2 studies ^c ; systematic reviews of level-2 studies
III	Level-3 studies ^d ; systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

^a Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

^b Level-1 studies are studies that use a blind comparison of the test with a validated reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

^c Level-2 studies are studies that have only one of the following:

- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case-control studies.

^d Level-3 studies are studies that have at least two or three of the features listed above.

Evidence was synthesised qualitatively by summarising the content of identified papers in a narrative manner with brief statements accurately reflecting the evidence and producing evidence tables. Quantitative synthesis (meta-analysis) was performed where appropriate.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables on the accompanying CD-ROM. Where possible, dichotomous outcomes are presented as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes are presented as weighted mean differences (WMDs) with 95% CIs.

1.7.3 Health economics

The aim of the economic input in this guideline was to inform the GDG of potential economic issues relating to the management of dehydration in children, and to ensure that recommendations represented a cost-effective use of scarce resources.

It is not possible to perform economic analysis for every clinical question and therefore some prioritisation is necessary, along the lines suggested in the NICE *Technical Manual*.²⁶ Some of the clinical questions do not involve a comparison of alternative courses of action (for example, What factors are associated with an increased risk of dehydration?) and are not amenable to economic analysis. For some questions addressing laboratory investigations, the GDG accepted that these often did not need to be routinely undertaken because such routine investigation would not be cost-effective, as they rarely affect management or health outcomes.

It was thought by the GDG that economic analysis would be important in formulating recommendations for the following two clinical questions:

- How do oral rehydration therapy (ORT) and intravenous fluid therapy (IVT) compare in terms of safety and efficacy, in the treatment of dehydration?
- Which interventions (other than fluid therapy and antibiotic treatment) are effective and safe?

The health economics for the latter question focused on oral ondansetron, an anti-emetic treatment.

A systematic search for published economic evidence was undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in decision-analytic modelling.³⁵ Reviews of the limited relevant published economic literature are presented as part of the appendix detailing the original economic analysis.

The primary economic focus in this guideline was on alternative fluid management therapy for children with dehydration. A decision-analytic model was developed to compare ORT with IVT. A simple economic analysis was also carried out in order to help guide recommendations on the use of ondansetron in vomiting children. The results of both analyses are summarised in the guideline text and a detailed description of the models has been included in Appendices A and B, respectively.

1.7.4 Forming and grading recommendations

The evidence tables, evidence overviews and summaries for the key clinical questions being discussed were made available to the GDG before the scheduled GDG meetings, and GDG members were expected to have read these in advance. For each clinical question, recommendations were derived using, and explicitly linked to, the evidence that supported them. Informal consensus methods were used by the GDG to agree evidence statements and recommendations, including the areas where important clinical questions were identified but no substantial evidence existed. The process by which the evidence statements informed the recommendations is summarised in a 'GDG translation' section in the relevant evidence review. Formal consensus methods were used to agree guideline recommendations and select eight key priorities for implementation.

1.7.5 External review

This guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholder organisations the opportunity to comment on the scope of the guideline at the initial stage of development and on the evidence and recommendations at the concluding stage. In addition, the guideline was peer reviewed.

1.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 4 years from date of publication. Reviewing may begin earlier than 4 years if significant evidence that affects guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

2 Summary of recommendations

2.1 Key priorities for implementation (key recommendations)

Chapter 3 Diagnosis

Perform stool microbiological investigations if:

- you suspect septicaemia or
- there is blood and/or mucus in the stool or
- the child is immunocompromised.

Chapter 4 Assessing dehydration and shock

Use Table 4.6 to detect clinical dehydration and shock.

Table 4.6 Symptoms and signs of clinical dehydration and shock

Interpret symptoms and signs taking risk factors for dehydration into account. Within the category of 'clinical dehydration' there is a spectrum of severity indicated by increasingly numerous and more pronounced symptoms and signs. For clinical shock, one or more of the symptoms and/or signs listed would be expected to be present. Dashes (–) indicate that these clinical features do not specifically indicate shock. Symptoms and signs with red flags (🚩) may help to identify children at increased risk of progression to shock. If in doubt, manage as if there are symptoms and/or signs with red flags.

Increasing severity of dehydration →			
	No clinically detectable dehydration	Clinical dehydration	Clinical shock
Symptoms (remote and face-to-face assessments)	Appears well	🚩 Appears to be unwell or deteriorating	–
	Alert and responsive	🚩 Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
	Normal urine output	Decreased urine output	–
	Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
	Warm extremities	Warm extremities	Cold extremities
Signs (face-to-face assessments)	Alert and responsive	🚩 Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
	Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
	Warm extremities	Warm extremities	Cold extremities
	Eyes not sunken	🚩 Sunken eyes	–
	Moist mucous membranes (except after a drink)	Dry mucous membranes (except for 'mouth breather')	–
	Normal heart rate	🚩 Tachycardia	Tachycardia
	Normal breathing pattern	🚩 Tachypnoea	Tachypnoea
	Normal peripheral pulses	Normal peripheral pulses	Weak peripheral pulses
	Normal capillary refill time	Normal capillary refill time	Prolonged capillary refill time
	Normal skin turgor	🚩 Reduced skin turgor	–
	Normal blood pressure	Normal blood pressure	Hypotension (decompensated shock)

Chapter 5 Fluid management

In children with gastroenteritis but without clinical dehydration:

- continue breastfeeding and other milk feeds
- encourage fluid intake
- discourage the drinking of fruit juices and carbonated drinks, especially in those at increased risk of dehydration
- offer oral rehydration salt (ORS) solution as supplemental fluid to those at increased risk of dehydration.

In children with clinical dehydration, including hypernatraemic dehydration:

- use low-osmolarity ORS solution (240–250 mOsm/l)* for oral rehydration therapy
- give 50 ml/kg for fluid deficit replacement over 4 hours as well as maintenance fluid
- give the ORS solution frequently and in small amounts
- consider supplementation with their usual fluids (including milk feeds or water, but not fruit juices or carbonated drinks) if they refuse to take sufficient quantities of ORS solution and do not have red flag symptoms or signs (see Table 4.6)
- consider giving the ORS solution via a nasogastric tube if they are unable to drink it or if they vomit persistently
- monitor the response to oral rehydration therapy by regular clinical assessment.

Use intravenous fluid therapy for clinical dehydration if:

- shock is suspected or confirmed
- a child with red flag symptoms or signs (see Table 4.6) shows clinical evidence of deterioration despite oral rehydration therapy
- a child persistently vomits the ORS solution, given orally or via a nasogastric tube.

If intravenous fluid therapy is required for rehydration (and the child is not hypernatraemic at presentation):

- use an isotonic solution, such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose, for both fluid deficit replacement and maintenance
- for those who required initial rapid intravenous fluid boluses for suspected or confirmed shock, add 100 ml/kg for fluid deficit replacement to maintenance fluid requirements, and monitor the clinical response
- for those who were not shocked at presentation, add 50 ml/kg for fluid deficit replacement to maintenance fluid requirements, and monitor the clinical response
- measure plasma sodium, potassium, urea, creatinine and glucose at the outset, monitor regularly, and alter the fluid composition or rate of administration if necessary
- consider providing intravenous potassium supplementation once the plasma potassium level is known.

Chapter 6 Nutritional management

After rehydration:

- give full-strength milk straight away
- reintroduce the child's usual solid food
- avoid giving fruit juices and carbonated drinks until the diarrhoea has stopped.

Chapter 10 Information and advice for parents and carers

Advise parents, carers and children that:[†]

- washing hands with soap (liquid if possible) in warm running water and careful drying is the most important factor in preventing the spread of gastroenteritis
- hands should be washed after going to the toilet (children) or changing nappies (parents/carers) and before preparing, serving or eating food

* The *BNF for Children* (BNFC) 2008 edition lists the following products with this composition: Dioralyte®, Dioralyte® Relief, Electrolade® and Rapolyte®.

† This recommendation is adapted from the following guidelines commissioned by the Department of Health: Health Protection Agency. *Guidance on Infection Control In Schools and other Child Care Settings*. London: HPA; 2006 [www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358374]
Working Group of the former PHLS Advisory Committee on Gastrointestinal Infections. Preventing person-to-person spread following gastrointestinal infections: guidelines for public health physicians and environmental health officers. *Communicable Disease and Public Health* 2004; 7(4):362–84.

- towels used by infected children should not be shared
- children should not attend any school or other childcare facility while they have diarrhoea or vomiting caused by gastroenteritis
- children should not go back to their school or other childcare facility until at least 48 hours after the last episode of diarrhoea or vomiting
- children should not swim in swimming pools for 2 weeks after the last episode of diarrhoea

2.2 Summary of recommendations

Chapter 3 Diagnosis

3.1 Clinical diagnosis

Suspect gastroenteritis if there is a sudden change in stool consistency to loose or watery stools, and/or a sudden onset of vomiting.

If you suspect gastroenteritis, ask about:

- recent contact with someone with acute diarrhoea and/or vomiting *and*
- exposure to a known source of enteric infection (possibly contaminated water or food) *and*
- recent travel abroad.

Be aware that in children with gastroenteritis:

- diarrhoea usually lasts for 5–7 days, and in most it stops within 2 weeks
- vomiting usually lasts for 1–2 days, and in most it stops within 3 days.

Consider any of the following as possible indicators of diagnoses other than gastroenteritis:

- fever:
 - temperature of 38 °C or higher in children younger than 3 months
 - temperature of 39 °C or higher in children aged 3 months or older
- shortness of breath or tachypnoea
- altered conscious state
- neck stiffness
- bulging fontanelle in infants
- non-blanching rash
- blood and/or mucus in stool
- bilious (green) vomit
- severe or localised abdominal pain
- abdominal distension or rebound tenderness.

3.2 Laboratory investigations

Consider performing stool microbiological investigations if:

- the child has recently been abroad *or*
- the diarrhoea has not improved by day 7 *or*
- there is uncertainty about the diagnosis of gastroenteritis.

Perform stool microbiological investigations if:

- you suspect septicaemia *or*
- there is blood and/or mucus in the stool *or*
- the child is immunocompromised.

Notify and act on the advice of the public health authorities if you suspect an outbreak of gastroenteritis.

If stool microbiology is performed:

- collect, store and transport stool specimens as advised by the investigating laboratory
- provide the laboratory with relevant clinical information.

Perform a blood culture if giving antibiotic therapy.

In children with *Escherichia coli* O157:H7 infection, seek specialist advice on monitoring for haemolytic uraemic syndrome.

Chapter 4 Assessing dehydration and shock

4.1 Clinical assessment

During remote or face-to-face assessment ask whether the child:

- appears unwell
- has altered responsiveness, for example is irritable or lethargic
- has decreased urine output
- has pale or mottled skin
- has cold extremities.

Recognise that the following are at increased risk of dehydration:

- children younger than 1 year, particularly those younger than 6 months
- infants who were of low birthweight
- children who have passed more than five diarrhoeal stools in the previous 24 hours
- children who have vomited more than twice in the previous 24 hours
- children who have not been offered or have not been able to tolerate supplementary fluids before presentation
- infants who have stopped breastfeeding during the illness
- children with signs of malnutrition.

Use Table 4.6 to detect clinical dehydration and shock.

Table 4.6 Symptoms and signs of clinical dehydration and shock

Interpret symptoms and signs taking risk factors for dehydration into account. Within the category of 'clinical dehydration' there is a spectrum of severity indicated by increasingly numerous and more pronounced symptoms and signs. For clinical shock, one or more of the symptoms and/or signs listed would be expected to be present. Dashes (–) indicate that these clinical features do not specifically indicate shock. Symptoms and signs with red flags (🚩) may help to identify children at increased risk of progression to shock. If in doubt, manage as if there are symptoms and/or signs with red flags.

Increasing severity of dehydration →			
	No clinically detectable dehydration	Clinical dehydration	Clinical shock
Symptoms (remote and face-to-face assessments)	Appears well	🚩 Appears to be unwell or deteriorating	–
	Alert and responsive	🚩 Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
	Normal urine output	Decreased urine output	–
	Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
	Warm extremities	Warm extremities	Cold extremities
Signs (face-to-face assessments)	Alert and responsive	🚩 Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
	Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
	Warm extremities	Warm extremities	Cold extremities
	Eyes not sunken	🚩 Sunken eyes	–
	Moist mucous membranes (except after a drink)	Dry mucous membranes (except for 'mouth breather')	–
	Normal heart rate	🚩 Tachycardia	Tachycardia
	Normal breathing pattern	🚩 Tachypnoea	Tachypnoea
	Normal peripheral pulses	Normal peripheral pulses	Weak peripheral pulses
	Normal capillary refill time	Normal capillary refill time	Prolonged capillary refill time
	Normal skin turgor	🚩 Reduced skin turgor	–
Normal blood pressure	Normal blood pressure	Hypotension (decompensated shock)	

Suspect hypernatraemic dehydration if there are any of the following:

- jittery movements
- increased muscle tone
- hyperreflexia
- convulsions
- drowsiness or coma.

4.2 Laboratory investigations for assessing dehydration

Do not routinely perform blood biochemical testing.

Measure plasma sodium, potassium, urea, creatinine and glucose concentrations if:

- intravenous fluid therapy is required *or*
- there are symptoms and/or signs that suggest hypernatraemia.

Measure venous blood acid–base status and chloride concentration if shock is suspected or confirmed.

Chapter 5 Fluid management

5.1 Primary prevention of dehydration

In children with gastroenteritis but without clinical dehydration:

- continue breastfeeding and other milk feeds
- encourage fluid intake
- discourage the drinking of fruit juices and carbonated drinks, especially in those at increased risk of dehydration
- offer oral rehydration salt (ORS) solution as supplemental fluid to those at increased risk of dehydration.

5.2 Treating dehydration

Use ORS solution to rehydrate children, including those with hypernatraemia, unless intravenous fluid therapy is indicated.

5.3 Optimal composition and administration of oral fluids

In children with clinical dehydration, including hypernatraemic dehydration:

- use low-osmolarity ORS solution (240–250 mOsm/l)* for oral rehydration therapy
- give 50 ml/kg for fluid deficit replacement over 4 hours as well as maintenance fluid
- give the ORS solution frequently and in small amounts
- consider supplementation with their usual fluids (including milk feeds or water, but not fruit juices or carbonated drinks) if they refuse to take sufficient quantities of ORS solution and do not have red flag symptoms or signs (see Table 4.6)
- consider giving the ORS solution via a nasogastric tube if they are unable to drink it or if they vomit persistently
- monitor the response to oral rehydration therapy by regular clinical assessment.

5.4 Intravenous fluid therapy

Use intravenous fluid therapy for clinical dehydration if:

- shock is suspected or confirmed
- a child with red flag symptoms or signs (see Table 4.6) shows clinical evidence of deterioration despite oral rehydration therapy
- a child persistently vomits the ORS solution, given orally or via a nasogastric tube.

* The *BNF for Children* (BNFC) 2008 edition lists the following products with this composition: Dioralyte®, Dioralyte® Relief, Electrolade® and Rapolyte®.

Treat suspected or confirmed shock with a rapid intravenous infusion of 20 ml/kg of 0.9% sodium chloride solution.

If a child remains shocked after the first rapid intravenous infusion:

- immediately give another rapid intravenous infusion of 20 ml/kg of 0.9% sodium chloride solution *and*
- consider possible causes of shock other than dehydration.

Consider consulting a paediatric intensive care specialist if a child remains shocked after the second rapid intravenous infusion.

When symptoms and/or signs of shock resolve after rapid intravenous infusions, start rehydration with intravenous fluid therapy

If intravenous fluid therapy is required for rehydration (and the child is not hypernatraemic at presentation):

- use an isotonic solution such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose, for fluid deficit replacement and maintenance
- for those who required initial rapid intravenous fluid boluses for suspected or confirmed shock, add 100 ml/kg for fluid deficit replacement to maintenance fluid requirements, and monitor the clinical response
- for those who were not shocked at presentation, add 50 ml/kg for fluid deficit replacement to maintenance fluid requirements, and monitor the clinical response
- measure plasma sodium, potassium, urea, creatinine and glucose at the outset, monitor regularly, and alter the fluid composition or rate of administration if necessary
- consider providing intravenous potassium supplementation once the plasma potassium level is known.

If intravenous fluid therapy is required in a child presenting with hypernatraemic dehydration:

- obtain urgent expert advice on fluid management
- use an isotonic solution such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose, for fluid deficit replacement and maintenance
- replace the fluid deficit slowly – typically over 48 hours
- monitor the plasma sodium frequently, aiming to reduce it at a rate of less than 0.5 mmol/l per hour.

Attempt early and gradual introduction of oral rehydration therapy during intravenous fluid therapy. If tolerated, stop intravenous fluids and complete rehydration with oral rehydration therapy.

5.5 Fluid management following dehydration

After rehydration:

- encourage breastfeeding and other milk feeds
- encourage fluid intake
- in children at increased risk of dehydration recurring, consider giving 5 ml/kg of ORS solution after each large watery stool. These include:
 - children younger than 1 year, particularly those younger than 6 months
 - infants who were of low birthweight
 - children who have passed more than five diarrhoeal stools in the previous 24 hours
 - children who have vomited more than twice in the previous 24 hours.

Restart oral rehydration therapy if dehydration recurs after rehydration.

Chapter 6 Nutritional management

During rehydration therapy:

- continue breastfeeding
- do not give solid foods
- in children with red flag symptoms or signs (see Table 4.6), do not give oral fluids other than ORS solution

- in children without red flag symptoms or signs (see Table 4.6), do not routinely give oral fluids other than ORS solution; however, consider supplementation with the child's usual fluids (including milk feeds or water, but not fruit juices or carbonated drinks) if they consistently refuse ORS solution.

After rehydration:

- give full-strength milk straight away
- reintroduce the child's usual solid food
- avoid giving fruit juices and carbonated drinks until the diarrhoea has stopped.

Chapter 7 Antibiotic therapy

Do not routinely give antibiotics to children with gastroenteritis.

Give antibiotic treatment to all children:

- with suspected or confirmed septicaemia
- with extra-intestinal spread of bacterial infection
- younger than 6 months with salmonella gastroenteritis
- who are malnourished or immunocompromised with salmonella gastroenteritis
- with *Clostridium difficile*-associated pseudomembranous enterocolitis, giardiasis, dysenteric shigellosis, dysenteric amoebiasis or cholera.

For children who have recently been abroad, seek specialist advice about antibiotic therapy.

Chapter 8 Other therapies

Do not use antidiarrhoeal medications.

Chapter 9 Escalation of care

During remote assessment:

- arrange emergency transfer to secondary care for children with symptoms suggesting shock (see Table 4.6)
- refer for face-to-face assessment children:
 - with symptoms suggesting an alternative serious diagnosis *or*
 - at high risk of dehydration, taking into account recognised risk factors *or*
 - with symptoms suggesting clinical dehydration *or*
 - whose social circumstances make remote assessment unreliable
- provide a 'safety net' for children who do not require referral. The safety net should include information for parents and carers on how to:
 - recognise developing red flag symptoms (see Table 4.6) *and*
 - get immediate help from an appropriate healthcare professional if red flag symptoms develop.

During face-to-face assessment:

- arrange emergency transfer to secondary care for children with symptoms or signs suggesting shock (see Table 4.6)
- consider repeat face-to-face assessment or referral to secondary care for children:
 - with symptoms and signs suggesting an alternative serious diagnosis
 - with red flag symptoms and/or signs of dehydration (see Table 4.6)
 - whose social circumstances require continued involvement of healthcare professionals
- provide a safety net for children who will be managed at home. The safety net should include:
 - information for parents and carers on how to recognise developing red flag symptoms (see Table 4.6) *and*
 - information on how to get immediate help from an appropriate healthcare professional if red flag symptoms develop *and*
 - arrangements for follow-up at a specified time and place, if necessary.

Chapter 10 Information and advice for parents and carers

10.1 Caring for a child with diarrhoea and vomiting at home

Inform parents and carers that:

- most children with gastroenteritis can be safely managed at home, with advice and support from a healthcare professional if necessary
- the following symptoms may indicate dehydration:
 - appearing to get more unwell
 - changing responsiveness (for example, irritability, lethargy)
 - decreased urine output
 - pale or mottled skin
 - cold extremities
- they should contact a healthcare professional if symptoms of dehydration develop.

Advise parents and carers of children:

- who are not clinically dehydrated and are *not* at increased risk of dehydration:
 - to continue usual feeds, including breast or other milk feeds
 - to encourage the child to drink plenty of fluids
 - to discourage the drinking of fruit juices and carbonated drinks
- who are not clinically dehydrated but who *are* at increased risk of dehydration:
 - to continue usual feeds, including breast or other milk feeds
 - to encourage the child to drink plenty of fluids
 - to discourage the drinking of fruit juices and carbonated drinks
 - to offer ORS solution as supplemental fluid
- with clinical dehydration:
 - that rehydration is usually possible with ORS solution
 - to make up the ORS solution according to the instructions on the packaging
 - to give 50 ml/kg ORS solution for rehydration plus maintenance volume over a 4 hour period
 - to give this amount of ORS solution in small amounts, frequently
 - to seek advice if the child refuses to drink the ORS solution or vomits persistently
 - to continue breastfeeding as well as giving the ORS solution
 - not to give other oral fluids unless advised
 - not to give solid foods.

Advise parents and carers that after rehydration:

- the child should be encouraged to drink plenty of their usual fluids, including milk feeds if these were stopped
- they should avoid giving the child fruit juices and carbonated drinks until the diarrhoea has stopped
- they should reintroduce the child's usual diet
- they should give 5 ml/kg ORS solution after each large watery stool if you consider that the child is at increased risk of dehydration.

Advise parents and carers that:

- the usual duration of diarrhoea is 5–7 days and in most children it stops within 2 weeks
- the usual duration of vomiting is 1 or 2 days and in most children it stops within 3 days
- they should seek advice from a specified healthcare professional if the child's symptoms do not resolve within these timeframes.

10.2 Preventing primary spread of diarrhoea and vomiting

Advise parents, carers and children that:*

- washing hands with soap (liquid if possible) in warm running water and careful drying are the most important factors in preventing the spread of gastroenteritis
- hands should be washed after going to the toilet (children) or changing nappies (parents/carers) and before preparing, serving or eating food
- towels used by infected children should not be shared
- children should not attend any school or other childcare facility while they have diarrhoea or vomiting caused by gastroenteritis
- children should not go back to their school or other childcare facility until at least 48 hours after the last episode of diarrhoea or vomiting
- children should not swim in swimming pools for 2 weeks after the last episode of diarrhoea.

2.3 Key priorities for research

Assessment for dehydration and shock (Chapter 4)

In children with gastroenteritis, what is the predictive value of clinical symptoms and signs in assessing the severity of dehydration, using post-rehydration weight gain as the reference standard, in primary and secondary care settings?

Why this is important

Evidence from a systematic review[†] suggests that some symptoms and signs (for example, prolonged capillary refill time, abnormal skin turgor and abnormal respiratory pattern) are associated with dehydration, measured using the accepted 'gold standard' of the difference between pre-hydration and post-hydration weight. However, 10 of the 13 included studies were not blinded and had ill-defined selection criteria. Moreover, all these studies were conducted in secondary care where children with more severe dehydration are managed.

Most children with gastroenteritis can and should be managed in the community[‡] but there is a lack of evidence to help primary care healthcare professionals correctly identify children with more severe dehydration. Symptoms and signs that researchers may wish to investigate include overall appearance, irritability/lethargy, urine output, sunken eyes, absence of tears, changes in skin colour or warmth of extremities, dry mucous membranes, depressed fontanelle, heart rate, respiratory rate and effort, character of peripheral pulses, capillary refill time, skin turgor and blood pressure.

Fluid management (Chapter 5)

In children who do not tolerate oral rehydration therapy, is ORS solution administration via nasogastric tube cost-effective, safe and acceptable in treating dehydration compared with intravenous fluid therapy?

Why this is important

Oral rehydration therapy is normally preferable to intravenous fluid therapy for rehydration in children with gastroenteritis. However, some children may not tolerate oral rehydration therapy, either because they are unable to drink ORS solution in adequate quantities or because they persistently vomit. In such cases, ORS solution could be administered via a nasogastric tube, rather than changing to intravenous fluid therapy. This overcomes the problem of ORS solution refusal. Continuous infusion of ORS solution via a nasogastric tube might reduce the risk of

* This recommendation is adapted from the following guidelines commissioned by the Department of Health: Health Protection Agency. *Guidance on Infection Control In Schools and other Child Care Settings*. London: HPA; 2006 [www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358374]
Working Group of the former PHLS Advisory Committee on Gastrointestinal Infections. Preventing person-to-person spread following gastrointestinal infections: guidelines for public health physicians and environmental health officers. *Communicable Disease and Public Health* 2004;7(4):362–84.

† Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? *JAMA: the Journal of the American Medical Association* 2004;291(22):2746–54.

‡ Hay AD, Heron J, Ness A; the ALSPAC study team. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. *Family Practice* 2005;22(4):367–74.

vomiting. A well-conducted randomised controlled trial is needed to assess the cost effectiveness, safety and acceptability of rehydration using nasogastric tube administration of ORS solution compared with intravenous fluid therapy.

Fluid management (Chapter 5)

In children who require intravenous fluid therapy for the treatment of dehydration, is rapid rehydration safe and cost-effective compared with the common practice of rehydration over 24 hours?

Why this is important

Most children with clinical dehydration should be treated with oral rehydration therapy, but some require intravenous fluid therapy because they are shocked or they cannot tolerate oral rehydration therapy. Rehydration with oral rehydration therapy is usually carried out over a period of 4 hours. Rehydration with intravenous fluid therapy has traditionally been undertaken slowly – typically over 24 hours. The National Patient Safety Agency has advised* that intravenous fluid deficit replacement should be over 24 hours or longer. Consequently, children will remain dehydrated and in hospital for a prolonged period. The WHO recommends that intravenous rehydration should be completed in 3–6 hours.† Many experts now support rapid intravenous rehydration, suggesting that it allows oral fluids to be started earlier and can shorten the duration of hospital treatment. Randomised controlled trials are needed urgently to examine the safety and cost-effectiveness of rapid intravenous rehydration regimens compared with slow intravenous rehydration.

Other therapies: ondansetron (Chapter 8)

In children with persistent vomiting caused by gastroenteritis, is oral ondansetron cost-effective and safe compared with placebo therapy?

Why this is important

Several randomised controlled trials have shown that in children with persistent vomiting during oral rehydration therapy, administration of oral ondansetron, an anti-emetic agent, can increase the likelihood of successful oral rehydration. However, in two of these there was evidence suggesting that diarrhoea was more pronounced in those given ondansetron than in those in the placebo groups. In one, in children given ondansetron, the number of stools passed during the rehydration phase was significantly greater, and in the other the number of stools passed in the first and second 24 hour period after rehydration was significantly greater. In those studies, diarrhoea was not a primary outcome, and it was reported as an adverse event. The reliability of the finding was therefore somewhat uncertain. If ondansetron does worsen diarrhoea it would be crucially important to determine the clinical significance of this effect, for example in relation to the risk of dehydration recurring or re-admission to hospital. If ondansetron is shown to be both effective and safe in secondary care then studies should also be undertaken to evaluate its use in primary care.

Other therapies: probiotics (Chapter 8)

Are probiotics effective and safe compared with a placebo in the treatment of children with gastroenteritis in the UK? Which specific probiotic is most effective and in what specific treatment regimen?

Why this is important

The available studies of probiotic therapy frequently report benefits, particularly in terms of reduced duration of diarrhoea or stool frequency. However, most of the published studies have methodological limitations. Moreover, there is great variation in the specific probiotics evaluated and in the treatment regimens used. Many of these studies were conducted in developing countries where the response to probiotic therapy may differ. Good-quality randomised controlled trials should be conducted in the UK to evaluate the effectiveness and safety of specific probiotics, using clearly defined treatment regimens and outcome measures.

* National Patient Safety Agency. Alert no. 22, Ref: NPSA/2007/22. Issued: 28 March 2007.

† World Health Organization. *The Treatment of Diarrhoea: a Manual for Physicians and Other Senior Health Workers*. Geneva: WHO; 2005 [whqlibdoc.who.int/publications/2005/9241593180.pdf].

2.4 Summary of research recommendations

Assessment for dehydration and shock (Chapter 4)

In children with gastroenteritis, what is the predictive value of clinical symptoms and signs in assessing the severity of dehydration, using post-rehydration weight gain as the reference standard, in primary and secondary care settings?

Fluid management (Chapter 5)

In children who do not tolerate oral rehydration therapy, is ORS solution administration via nasogastric tube cost-effective, safe and acceptable in treating dehydration compared with intravenous fluid therapy?

In children who require intravenous fluid therapy for the treatment of dehydration, is rapid rehydration safe and cost-effective compared with the common practice of rehydration over 24 hours?

Other therapies (Chapter 8)

In children with persistent vomiting caused by gastroenteritis, is oral ondansetron cost-effective and safe compared with placebo therapy?

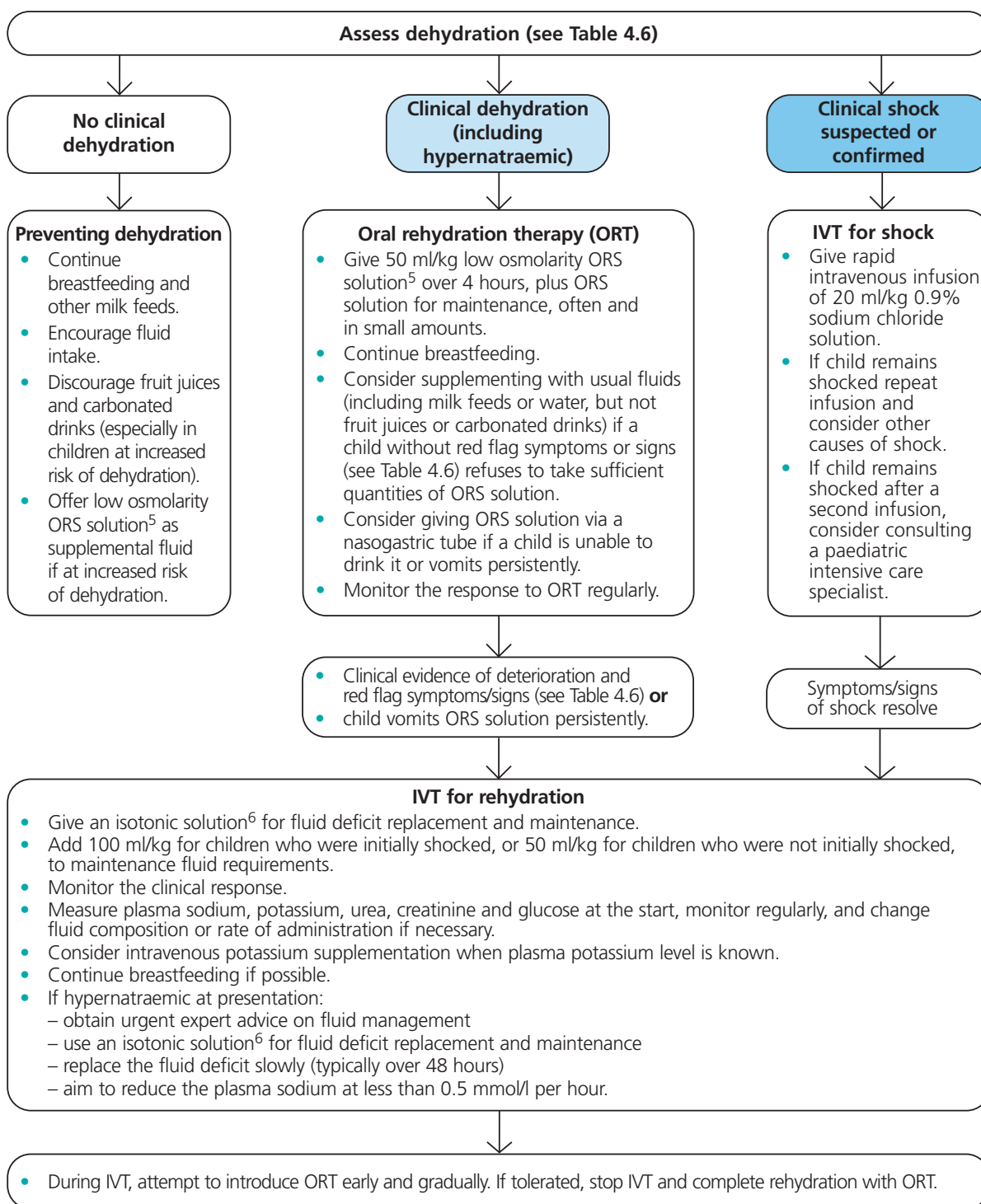
Is racecadotril (an enkephalinase inhibitor) cost-effective and safe in the treatment of gastroenteritis in children compared with a placebo?

Are probiotics effective and safe compared with a placebo in the treatment of children with gastroenteritis in the UK? Which specific probiotic is most effective and in what specific treatment regimen?

2.5 Flow pathway for fluid management

The fluid management flow pathway overleaf is reproduced (with minor amendment of the cross-references) from the NICE Quick Reference Guide version of this guideline (www.nice.org.uk/CG84quickrefguide).

Fluid management



⁵ 240–250 mOsm/l. The 'BNFC' 2008 edition lists the following products with this composition: Dioralyte, Dioralyte Relief, Electrolade and Rapolyte.

⁶ Such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose.

3 Diagnosis

Many children experience brief episodes of vomiting and diarrhoea due to mild gastroenteritis and are managed by their parents at home. Parents may not approach a healthcare professional at all. However, many do seek advice either 'remotely' (for example, NHS Direct) or through a face-to-face consultations. When children present to a healthcare professional, it is important to establish whether or not they truly have diarrhoea or vomiting. This chapter reviews the relevant published evidence and provides recommendations regarding the clinical and laboratory diagnosis of gastroenteritis. These recommendations are intended to take account of the particular setting in which the child presents, for example in the community, the general practitioner's surgery, or the hospital emergency department.

3.1 Clinical diagnosis

Introduction

The sudden onset of diarrhoea with or without vomiting in a previously well child is usually due to gastroenteritis. The definition of diarrhoea may seem to be self-evident but, even in well infants and children, stool frequency and consistency vary considerably. For example, breastfed infants may have more frequent and softer stools than bottle-fed infants. Even in older children, confusion may occur – those with overflow faecal incontinence due to constipation are often mistakenly reported to have diarrhoea.

Vomiting may occur before the onset of diarrhoea. However, vomiting in isolation may be due to a wide range of other potentially serious conditions. In infants, vomiting must be distinguished from the normal phenomenon of regurgitation.

Although most children with acute-onset diarrhoea have gastroenteritis, occasionally it may occur in association with other disorders, such as non-gastrointestinal infections (for example, pneumonia), and surgical conditions (for example, acute appendicitis). In 2007, 7600 children presented to a paediatric emergency unit in England with suspected acute gastroenteritis.³⁶ Of these, 60% were discharged for home treatment. A total of 3022 were admitted to an observation ward, and only 106 of these were subsequently transferred to a medical or surgical ward. Those children had a range of diagnoses, including gastroenteritis, non-specific abdominal pain, appendicitis and constipation. Other diagnoses were rare but included such diverse conditions as non-infective colitis, malabsorption, intestinal obstruction, inguinal hernia and pyloric stenosis.

Even when a presumptive diagnosis of gastroenteritis has been made at the outset, it is important to reconsider the diagnosis if the subsequent course of the illness is inconsistent with the condition.

This chapter gives recommendations regarding practical definitions for diarrhoea and vomiting, identifies key clinical pointers to conditions other than gastroenteritis and provides information on the natural history of the disease.

Clinical question

What definitions of diarrhoea and vomiting have been used previously?

Research studies on the incidence of gastroenteritis have employed various arbitrary definitions of diarrhoea based on the stool frequency and/or consistency. A change in these variables in the individual child has also been considered to be an important consideration. Examples of definitions that have been employed are listed below.

- Diarrhoea is defined as a change in bowel habit for the individual child resulting in substantially more frequent and/or looser stools.¹⁷
- Diarrhoea in children is the passage of unusually loose or watery stools, usually at least three times in 24 hours. It is acute if it has persisted for less than 10–14 days.²⁰

- Diarrhoea is an alteration in normal bowel movement characterised by an increase in the water content, volume or frequency of stools. A decrease in consistency (i.e. soft or liquid) and an increase in frequency of bowel movements to three or more stools per day have often been used as a definition for epidemiological investigations.³⁷
- In diarrhoea, stools contain more water than normal – they are also called loose or watery stools. They may also contain blood, in which case the diarrhoea is called dysentery. Acute diarrhoea starts suddenly and may continue for several days. It is caused by infection of the bowel.³⁸

There is less variation regarding definitions of vomiting. It has been defined as the ejection of gastric contents up to and out of the mouth, brought about by a forceful contraction of the abdominal muscles and diaphragm.³⁹

For the purpose of this guideline, the GDG thus decided to use the following definitions:

‘Diarrhoea refers to the passage of liquid or watery stools. In most cases there is an associated increase in stool frequency and volume.’

‘Vomiting is the forceful ejection of the stomach contents up to and out of the mouth.’

The GDG considered that, in children with gastroenteritis, the occurrence of diarrhoea is readily apparent from the sudden change in stool consistency to loose or watery stools. It is often associated with an increase in stool frequency, although this may not yet be evident at the time of presentation. Vomiting is partly a voluntary action and partly an involuntary reflex, and is characterised by the forceful ejection of gastric contents up to and from the mouth. Regurgitation is common in infants but is a recurring phenomenon and so can usually be distinguished from sudden onset vomiting due to gastroenteritis.

Recommendation on clinical diagnosis

Suspect gastroenteritis if there is a sudden change in stool consistency to loose or watery stools, and/or a sudden onset of vomiting.

Clinical question

What is the usual duration of diarrhoea and vomiting in children with gastroenteritis?

It was important to establish the usual duration of vomiting and diarrhoea in children with gastroenteritis. Persistence of diarrhoea for a longer period of time than expected might be an important pointer to an alternative diagnosis, for example a non-infectious gastrointestinal disorder such as coeliac disease. This information would also be important, however, when advising parents about the likely outcome of the illness, and how soon recovery might reasonably be expected.

Evidence overview

Many observational studies identified during the literature search did not provide data on the duration of diarrhoea and vomiting in children or they failed to differentiate between whether the reported duration was prior to study entry or during the study period. In other studies, some children were given treatment but the authors failed to provide information separately for the group which did not receive treatment. Hence information to answer this question was obtained predominantly from control subjects in RCTs. A total of 11 studies were included, six of which provided information on the duration of diarrhoea and five on vomiting. Two of these 11 studies were conducted in the UK.

Of the studies relevant to diarrhoea, five were conducted in a hospital setting and one in a primary care setting. Data on the mean duration of diarrhoea were obtained from the control subjects in four RCTs^{40–43} conducted in Poland, Israel, Colombia and South Africa. The sample size in these RCTs ranged from 28 to 120. Further information was obtained from a cross-sectional study from Kuwait,⁴⁴ in which almost 50% of the children ($n = 595$) had bacterial infections. Unfortunately, the data in the Kuwait study was presented without standard deviation values. The primary-care-based study⁴⁵ was a small RCT from Denmark ($n = 19$) that recruited participants with acute diarrhoea from a day-care centre. The results are presented in Table 3.1.

Table 3.1 Duration of diarrhoea in children

Study	Setting	Sample size	Mean duration of diarrhoea during study period Days (SD)
Szymanski <i>et al.</i> (2006) ⁴⁰	Hospital	41	4.0 ± 3.0
Gazala <i>et al.</i> (1988) ⁴¹	Hospital	53	3.7 ± 1.9
Lozano <i>et al.</i> (1994) ⁴²	Hospital	28	2.3 ± 1.7
Haffejee (1990) ⁴³	Hospital	120	2.9 ± 2.3
Khuffash <i>et al.</i> (1988) ⁴⁴	Hospital	595	7.4 (SD not given)
Rosenfeldt <i>et al.</i> (2002) ⁴⁵	Community	19	4.8 ± 3.5

Data on the mean duration of vomiting prior to hospital admission was given in three RCTs: 2.4 days (range 1–6),⁴⁶ 1.6 days (SD 1.2)⁴⁷ and 2.5 days (SD 1.7).⁴⁸ These RCTs were conducted in Australia ($n = 59$), Saudi Arabia ($n = 150$) and Finland ($n = 65$), respectively. Two small RCTs conducted in the UK provided data on vomiting during the hospital stay. In one RCT,⁴⁹ the numbers of children with vomiting on days 1, 2 and 3 were 7/16, 3/16 and 2/16, respectively. In the other RCT,⁵⁰ it was reported that, of 14 children, none experienced any vomiting over 4 days.

Evidence summary

Evidence for this question was marked by great variation among the studies regarding the settings, sample sizes and study period. In the five hospital-based studies, the mean duration of diarrhoea from the time of presentation ranged from 2.3 to 7.4 days. In the small community-based study, more than 60% of the children presenting with diarrhoea to a clinic recovered from the condition by day 5.

In three RCTs, the mean duration of vomiting prior to hospital admission varied from 1.6 to 2.5 days. Data from two small hospital-based RCTs indicated that vomiting had ceased in most patients within 2 or 3 days of admission.

GDG translation from evidence to recommendation

The GDG noted the lack of satisfactory data from the UK regarding the duration of diarrhoea and vomiting in children with gastroenteritis. The available data were obtained from clinical trials in which measurement of symptom duration was not the primary aim of the study. Many of the studies measured duration of diarrhoea only during the period of hospital admission, and so underestimation may have occurred. The only study based in a primary care setting was very small. Those members of the GDG with experience of managing gastroenteritis in the community believed that diarrhoea usually resolves within 5–7 days but occasionally may persist till 14 days. That view is consistent with the data presented in Table 3.1.

Recommendation on duration of diarrhoea and vomiting

Be aware that in children with gastroenteritis:

- diarrhoea usually lasts for 5–7 days, and in most it stops within 2 weeks
- vomiting usually lasts for 1–2 days, and in most it stops within 3 days.

Clinical question

What factors influence the natural history of gastroenteritis?

Five relevant studies were identified to address this question. Four cross-sectional studies with EL = 3 reported on the clinical features associated with various infective pathogens^{51–44} and three of them were conducted in Europe. The fourth study is a case-control study [EL = 2+] from India reporting on the risk factors for persistent diarrhoea.⁵⁴

Evidence overview

Clinical features associated with infective pathogens

In a prospective cross-sectional study from Sweden,⁵¹ the clinical features associated with bacterial and viral gastroenteritis were compared in children ($n = 393$) presenting to the hospital. The study focused on duration and frequency of symptoms, fever and abdominal pain, and duration of hospital stay. Infection with rotavirus was characterised by sudden onset of vomiting, a high incidence of fever and dehydration and a mean duration of diarrhoea of 5.9 days. Enteric adenovirus was associated with longer lasting diarrhoea, with a mean of 10.8 days. Bacterial infections were associated with abdominal pain, bloody diarrhoea, prolonged diarrhoea (mean 14.1 days), leucocytosis and a raised erythrocyte sedimentation rate (ESR). [EL = 3]

In the second hospital-based prospective cross-sectional study from Italy,⁵² the clinical features at presentation were compared in 215 children with viral and bacterial gastroenteritis. Enteric pathogens were detected in 127/215 (59%) cases with viral infections accounting for almost 80% of these (single or double viral or co-infection with bacterial pathogens) while mono-bacterial infections were detected in the rest. No sample was positive for parasites. Vomiting and dehydration were more frequent in children with viral gastroenteritis ($P < 0.01$) compared with those without viral infection. The severity of dehydration (assessed by a 14-point severity score) was significantly higher in children infected with either astrovirus or rotavirus group A. Prolonged hospitalisation was also more likely to occur with rotavirus infection. [EL = 3]

A prospective UK study⁵³ included 1148 children younger than 16 years admitted to a sub-regional infectious disease hospital with a diagnosis of gastroenteritis over a 1 year period. Of the admitted children, 55% (635/1148) were younger than 1 year while 5% were over 5 years of age. Admissions were predominantly from socially disadvantaged families (62% from social classes IV and V). At the time of admission, 8.8% (101/1148) of children were clinically dehydrated, with 1% assessed to have greater than 5% dehydration. Seventy-nine percent of children had a history of vomiting before admission and it was more common with rotavirus infection than bacterial pathogens (92% versus 54%; $P < 0.001$). Diarrhoea of bacterial, protozoal or mixed aetiology had a higher incidence of stool containing blood and/or mucus compared with rotavirus, and abdominal pain was more common in bacterial diarrhoea than diarrhoea of other aetiology ($P < 0.001$ for both). During the hospital stay, diarrhoea persisted for longer duration in children with bacterial, protozoal or mixed aetiology than in those with rotavirus. Fifty-two percent of rotavirus cases settled within 48 hours of admission compared with 39% for the other group, while 16% of the rotavirus group had diarrhoea persisting beyond 96 hours of admission compared with 31% for the other group ($P < 0.05$ for both comparisons). This study also gave information on the incidence of enteric pathogens and biochemical abnormalities detected during laboratory investigations, and that information has been included under the relevant sections. [EL = 3]

In a cross-sectional study from Kuwait,⁴⁴ the duration of diarrhoea and clinical characteristics associated with various pathogens were examined. In total, 595 children (age range under 1 year to 12 years) admitted to the hospital with gastroenteritis were included. Two stool specimens were collected within 18 hours of admission to determine the pathogens responsible for gastroenteritis. Rotavirus was the most common pathogen detected, in 45% of children (34% pure isolates and the rest in combination with bacteria), followed by salmonella in 24% of children (17% pure isolates and 7% in combination with rotavirus). The mean duration of diarrhoea was longer in those with salmonella (12.3 days) than in those with rotavirus (4.8 days) or other bacterial pathogens detected alone or in combination with other infections (mean duration ranging from 6.8 to 7.9 days) (Table 3.2). Gastroenteritis with rotavirus infection had a self-limiting course with no mortality and low morbidity and was associated with few extra-intestinal manifestations, while salmonella infections had the highest frequency of milk intolerance (31%), malnutrition (36%), and associated features (convulsions in 20% and septicaemia in 17%). Abdominal pain and bloody diarrhoea were common in infections with shigella, salmonella and campylobacter. Features of extra-intestinal invasions (such as toxic look, fever > 3 days, poor feeding, hepatosplenomegaly and pneumonia) were seen almost exclusively in children with salmonella infections. [EL = 3]

Risk factors for persistent diarrhoea

A case-control study from India⁵⁴ investigated possible risk factors for persistent diarrhoea (>14 days). They compared 170 cases with 340 controls (aged 1–23 months) who had been

Table 3.2 Duration of diarrhoea in 595 children with gastroenteritis^{a 44}

Clinical study group	Number	Mean duration (days)
Rotavirus	203 (34%)	4.8
Salmonellae	98 (16%)	12.3
<i>Escherichia coli</i>	55 (9%)	6.8
Campylobacter	36 (6%)	7.4
Shigellae	22 (4%)	7.9
Rotavirus and salmonellae	44 (7%)	12.9
Rotavirus and others	26 (4%)	7.4
No pathogen	111 (19%)	5.6
Total	595 (100%)	7.4

^a Five children with *Aeromonas hydrophila* were excluded from the analysis.

admitted to hospital. Cases were children with diarrhoea persisting for more than 14 days while the controls had all recovered within 7 days of admission. For each case, two age-matched controls were recruited. If the controls became cases either during hospital stay or follow-up, they were withdrawn and fresh controls recruited. The episode of diarrhoea was considered to be controlled when a child had no diarrhoea for 2 consecutive days. Fifteen potential risk factors were examined. After adjusting for co-variables by multiple logistic regression analysis, the factors independently associated with persistent diarrhoea were malnutrition (adjusted OR 2.9; 95% CI 1.9 to 4.5), stool with blood and/or mucus (adjusted OR 2.4; 95% CI 1.3 to 4.3), indiscriminate use of antibiotics (adjusted OR 2.4; 95% CI 1.6 to 3.9), stool frequency more than 10 per day (adjusted OR 1.8; 95% CI 1.2 to 2.8) and persistence of dehydration for more than 24 hours (adjusted OR 1.4; 95% CI 1.2 to 1.7). [EL = 2+]

Evidence summary

Results from three cross-sectional studies [EL = 3] suggested that viral gastroenteritis was associated with a shorter duration of diarrhoea than bacterial gastroenteritis. The fourth cross-sectional study from Italy did not report the duration separately for the viral and bacterial infections. There was consistent evidence from these studies to indicate that vomiting and dehydration were more common with viral gastroenteritis while bloody diarrhoea and abdominal pain were more often associated with bacterial gastroenteritis. A case-control study [EL = 2+] reported that malnutrition, bloody and/or mucoid stools, indiscriminate use of antibiotics, high stool frequency (>10 per day), and persistence of dehydration (>24 hours) were factors independently associated with an increased risk of persistent diarrhoea.

GDG translation from evidence to recommendation

Several cross-sectional studies have provided consistent evidence of differences in the manifestations of viral and bacterial gastroenteritis. Viral gastroenteritis is of shorter duration than bacterial gastroenteritis and associated with an increased risk of vomiting and dehydration. Bacterial gastroenteritis is more often associated with severe abdominal pain and sometimes with bloody diarrhoea.

While the GDG recognised that the study of risk factors for persistent diarrhoea was based on a population in India, the findings were nevertheless important, especially given the multi-ethnic composition of the UK population and the increasing frequency of overseas travel. Some potentially important risk factors for persistent diarrhoea were identified: persistence of dehydration for more than 24 hours after appropriate fluid therapy, presence of blood and/or mucus in the stool, stool frequency greater or equal to 10 per day, indiscriminate use of antimicrobials, weight loss and poor nutritional status.

Clinical question

In children presenting with diarrhoea and/or vomiting, what characteristics may suggest a diagnosis other than gastroenteritis?

Acute diarrhoea is not always due to an intestinal infection. Other non-enteric infections and non-infective gastrointestinal disorders may be responsible. Diarrhoea is a common side effect of antibiotic therapy. Many other drugs and certain dietary constituents (for example, sorbitol and xylitol), may occasionally be responsible and on rare occasions certain toxins (for example, organophosphate insecticides).⁵⁵

Evidence overview

In the absence of comparative studies, the literature search for this question was undertaken to identify case series with sample sizes more than 100. Another source of information was the NICE published guideline *Feverish illness in children*.⁵⁶ It had recommended signs and symptoms for identifying children with fever who are at high risk for serious illness. The list of various alternative diagnoses based upon the published evidence and the consensus view of the GDG are given in Table 3.3.

GDG translation from evidence to recommendation

Based on consensus, the GDG identified a number of key points that they considered were important in the history and examination of the child. It would be important to be aware of any history of contact with an individual with symptoms of gastroenteritis. Also, exposure of the child to a known source of enteric infection or a history of recent travel abroad would be important. Certain symptoms and signs might point to diagnosis other than gastroenteritis. For example, although fever may occur in children with gastroenteritis, high fever is somewhat unusual. Therefore the possibility of other disorders would require careful consideration in such cases.

Table 3.3 Key symptoms and signs in the differential diagnosis of children presenting with diarrhoea and/or vomiting^a

Alternative diagnosis	Key symptoms	Key signs ^b
<i>Non-enteric infections:</i>		
• pneumonia	Cough, shortness of breath, chest pain	Tachypnoea, tachycardia
• urinary tract infection	Frequency and dysuria	
• meningitis	Persistent vomiting, altered consciousness, irritability, photophobia	Petechial purpuric rash, neck stiffness, bulging fontanelle in infants
• acute otitis media	Earache	
• toxic shock syndrome	Non-specific muscle aches, faintness	Clinical shock, red non-specific rash, possible site of bacterial entry such as small burn or injury
<i>Non-infective gastrointestinal disorders:</i>		
• ulcerative colitis, Crohn's disease or coeliac disease	Prolonged diarrhoea (>14 days), bloody diarrhoea	Failure to thrive or weight loss
<i>Surgical disorders:</i>		
• Bowel obstruction, intussusceptions or ischaemic bowel	Bilious vomiting, severe or localised abdominal pain, bloody diarrhoea	Abdominal distension, rebound tenderness, mucoid/bloody stools
<i>Drug-related:</i>		
Review drug history (e.g. antibiotic therapy)		

^a Children younger than 12–18 months commonly present with non-specific symptoms and signs of non-enteric infections and non-infective gastrointestinal disorders.

^b High fever (temperature $\geq 38\text{ }^{\circ}\text{C}$ for children younger than 3 months and $\geq 39\text{ }^{\circ}\text{C}$ for children 3 months or older) may occur in gastroenteritis, but may also be a pointer to non-enteric infections.

The GDG also considered that the main conditions in the differential diagnosis of gastroenteritis include non-enteric infections, non-infective gastrointestinal disorders, abdominal surgical disorders and antibiotic-associated diarrhoea. It was agreed that, if vomiting persisted for more than 24 hours without diarrhoea, diagnoses other than gastroenteritis (for example, urinary tract infection) should be considered.

Recommendations on diagnosis

If you suspect gastroenteritis, ask about:

- recent contact with someone with acute diarrhoea and/or vomiting *and*
- exposure to a known source of enteric infection (possibly contaminated water or food) *and*
- recent travel abroad.

Consider any of the following as possible indicators of diagnoses other than gastroenteritis:

- fever:
 - temperature of 38 °C or higher in children younger than 3 months
 - temperature of 39 °C or higher in children aged 3 months or older
- shortness of breath or tachypnoea
- altered conscious state
- neck stiffness
- bulging fontanelle in infants
- non-blanching rash
- blood and/or mucus in stool
- bilious (green) vomit
- severe or localised abdominal pain
- abdominal distension or rebound tenderness.

3.2 Laboratory investigations in diagnosis

Introduction

Most children with gastroenteritis do not require any laboratory investigations. Many infants and children experience brief episodes of diarrhoea and are managed by their parents without seeking professional advice. Even if advice is sought, healthcare professionals often consider that a clinical assessment is all that is required, and laboratory investigations are not undertaken. However, there may be particular circumstances when investigations may be helpful in diagnosis.

3.2.1 Stool microbiological investigation

In clinical practice, most children with gastroenteritis do not undergo any stool investigations and no attempt is made to identify the presumptive enteric pathogen. In some cases, however, microbiological investigation may be appropriate. There might be circumstances in which identification would be important. Some pathogens are of special significance. For example, amoebic dysentery would require antimicrobial therapy. *Escherichia coli* O157:H7 is associated with a risk of haemolytic uraemic syndrome (HUS) – a serious and potentially deadly disorder. Bloody diarrhoea may be caused by serious non-infective conditions such as inflammatory bowel disease (ulcerative colitis or Crohn’s disease) and isolation of a bacterial pathogen might therefore be diagnostically helpful.

It was therefore important to determine the frequency with which enteric pathogens were identified by stool microbiological investigation. An additional group for consideration was the child with diarrhoea recently returned from overseas travel in whom the likely pathogens might differ.

Clinical question

In what proportion of children with a clinical diagnosis of gastroenteritis is a causative enteric pathogen identified? What is the incidence of specific pathogens?

It was important to first determine how frequently enteric pathogens can be found in children with gastroenteritis in the UK. The evidence to inform this question was taken from eight published studies from England and Wales and the website of the Health Protection Agency (HPA).

Evidence overview

The first three studies^{53,57,58} gave information on the proportion of children with enteric pathogens isolated but all these studies were hospital based and conducted before 1990. Of the remaining studies, four^{59–62} gave information on viral pathogens isolated in children with gastroenteritis but they all provided regional data. The last published paper¹¹ is a population-based study comparing the incidence of gastroenteritis in the community with that in patients presenting to their general practitioner, but in this paper the study population included both adults and children. Since no published data were available for the overall incidence of enteric pathogens in children with gastroenteritis from England and Wales, this information was collected from the website of the UK HPA (www.hpa.org.uk).

A prospective study⁵³ included 1148 children younger than 16 years admitted to a sub-regional infectious disease hospital with a diagnosis of gastroenteritis over a 1 year period (1986–87). The demographic characteristics of the study population have been described in detail in Section 3.1 above. In this study, 8.8% of children (101/1148) were clinically dehydrated, with 1% assessed to have greater than 5% dehydration. Dehydrated children were more likely to have an enteric pathogen identified compared with those without clinical dehydration (61% versus 43%; $P < 0.001$). Stool examination identified enteric pathogens in altogether 44.6% of cases (512/1148), with rotavirus being the most common (in 31%). The common bacterial pathogens isolated were salmonella spp. (5%), campylobacter spp. (3.2%), and enteropathogenic *E. coli* (2%), while cryptosporidium (1.4%) was the most common protozoal organism detected. [EL = 3]

The second study was a prospective survey⁵⁷ that recruited 447 children younger than 2 years and admitted to a hospital with gastroenteritis over a 1 year period (1981–82). Seventy-four percent of the children were younger than 1 year and two-thirds of under-1-year-olds were younger than 6 months. Pathogenic enteric organisms were isolated in 75% of cases (335/447), with viruses alone in 57%, bacteria alone in 6% and both viruses and bacteria isolated in 10% of cases. Rotavirus was the most common organism isolated, in 34% of cases (152/447), while all other viruses were detected in 53% of children. Enteropathogenic *E. coli* (6.9%), *Campylobacter jejuni* (5.1%), *Clostridium difficile* toxin (4.9%), salmonella spp. (4.3%) and shigella spp. (2%) were the main bacteria isolated. [EL = 3]

The third study⁵⁸ included 215 children admitted to four paediatric units in south Wales with gastroenteritis over a 1 year period (1987–88). The age of the study population ranged from 2 weeks to 9 years and 61% of children were younger than 1 year. The primary aim of the study was to describe the clinical characteristics, incidence of complications, and management (pre-admission and hospital) of the patients. The authors did not specify the total number of cases with clinical dehydration, but overall only 7% were judged to be severely dehydrated. Pathogenic organisms were isolated in the stools of 58% of children (125/215) with virus alone in 30% (65/215). Among the viral pathogens, rotavirus was the most frequently isolated (83% of all viruses). Bacteria alone were found in 14% of cases, with campylobacter and *E. coli* being the most common. Cryptosporidium spp. were the most common parasites detected. [EL = 3]

A surveillance study⁵⁹ reported viral agents isolated from clinical specimens in a regional public health laboratory in the UK during the winter of 1999–2000. Altogether 3172 specimens (stool or occasional vomit) of sporadic cases of gastroenteritis in children under the age of 7 years were sent to the laboratory. Samples were received from general practitioners (34%), hospitals (56%) and other public laboratories (9%) in the southwest of England and south Wales. Over the same period, 1360 specimens were also tested from 285 reported outbreaks of gastroenteritis, with 34% of these specimens coming from the community and the rest from the hospitals. A viral aetiology was confirmed in 37.7% of sporadic cases of gastroenteritis, with rotavirus being the most common viral agent detected, in 21.6% (685/3172) of them. The other enteric viruses detected were norovirus (10.3%), adenovirus (3.9%), astrovirus (3.1%) and calicivirus (0.2%). The prevalence of all the enteric viral agents was reported to be higher in the specimens from the community compared with the specimens from the hospitals. For the outbreaks, norovirus was the most common viral agent isolated (in 63.9% of outbreaks), followed by rotavirus (3.9%), adenovirus (0.4%) and astrovirus (0.4%). No viral agent was isolated in 32.6% of outbreaks. [EL = 3]

In another prospective study from a large hospital,⁶⁰ stool samples of children (younger than 16 years) admitted to the hospital with a diagnosis of acute gastroenteritis or who developed

the condition following hospitalisation were examined. Gastroenteritis was considered to be healthcare associated if symptoms developed 48 hours or more following admission. The study included a total of 243 subjects (87% of eligible subjects) who had clinical data and a stool specimen collected during the 5 month study period, and 37% (91/243) of these cases were judged to be healthcare associated while the rest were diagnosed to have community-acquired infection. Rotavirus was detected in altogether 29% of cases (71/243). The proportion of community-acquired cases testing positive for rotavirus was 36% (54/152), while for healthcare-associated cases the proportion was 19% (17/91). [EL = 3]

In the sixth study, conducted in East Anglia, England,⁶² stool samples collected during three consecutive winter seasons (2000–2003) were tested for the presence of viral pathogens. The sample population comprised 685 children younger than 6 years with symptoms of gastroenteritis: 223 children presenting to a general practitioner (part of a structured surveillance study evaluating burden of disease), 203 children referred by various general practices in the community to the hospital, and 259 children admitted to the hospital as inpatients or attending the accident and emergency department. A viral agent was detected in 53.4% of samples (366/685). A significantly greater number of children from the structured surveillance study group had a viral pathogen detected in their stool specimen compared with the community cohort (68.6% versus 51.2%; $P < 0.05$) or the hospital cohort (68.6% versus 42.1%; $P < 0.05$). The proportion of children from the community with a viral agent detected was also significantly higher compared with children in the hospital cohort (51.2% versus 42.1%; $P < 0.05$). Rotavirus was the most common pathogen isolated in each of the three cohorts: 40.4% in the structured surveillance study, 24.6% in the community cohort and 17.8% in the hospital cohort. The second most common viral pathogen isolated was norovirus in the surveillance study group (9.9%) and the hospital cohort group (9.7%), while in the community cohort group it was enteric adenovirus (8.9%). Multiple viral pathogens were detected in 8% of the samples and most of these (72.7%) involved rotavirus in combination with other viruses. [EL = 3]

As part of a prospective, multicentre study on the incidence of rotavirus in Europe,⁶¹ 1010 stool samples were examined from children younger than 5 years who presented with gastroenteritis to a regional health service in the UK in the winter of 2004–2005. The results were reported in relation to the clinical setting in which they were seen: primary care (general practitioners and/or paediatricians), emergency department and hospital admission. The overall percentage of children with rotavirus-positive gastroenteritis was estimated to be 35.9%, with the incidence being almost the same for the two groups of children seen in the emergency department and hospital (60.0% and 60.7%, respectively). In a primary care setting, rotavirus was isolated in 31.9% of the samples. [EL = 3]

The last study was a population-based study¹¹ undertaken to evaluate the incidence and aetiology of infectious intestinal disease in both adults and children presenting to general practitioners and in the community, and to establish how many of them are reported to the national laboratory-based surveillance. The study cohort included a population of 459 975 patients registered with 70 general practices in England, and this selected sample of population was representative of all the general practices nationally with respect to geographical location, urban and rural characteristics, and social deprivation index. To calculate incidence in the community, 200 people were randomly recruited from each general practice out of which 9776 people (an average of 140 people from each general practice) agreed to participate. These people were asked to return weekly postcards for 6 months declaring the absence of symptoms, and those with symptoms were asked to send a stool specimen to a public health laboratory. Eighty-two percent of the participants returned 22 or more of the 26 weekly postcards. For the general practice incidence data, all cases of infectious intestinal disease presenting to a general practitioner were eligible for inclusion irrespective of their age. The practices were randomly allocated to two arms: in the first arm, all patients (34 general practices) were asked to send stool specimens to a public health laboratory, while in the second arm (36 general practices), stool testing was conducted locally and information sought from the national surveillance database on those with a positive stool specimen. This step was taken to evaluate the completeness of the reporting system.

In the community, 781 cases were ascertained for infectious intestinal disease, with an incidence of 19.4 per 100 person-years (95% CI 18.1 to 20.8), while 8770 people presented to their general practice giving an incidence of 3.3 per 100 person-years (95% CI 2.94 to 3.75). The ratio of

community incidence to general practice presentation was 5.8, suggesting that, for every case presenting to general practice with intestinal disease, almost six more cases were present in the community. The ratio was high for cases associated with *E. coli* non-O157, yersinia, rotavirus group C, *C. difficile* cytotoxin, aeromonas and for cases where no organism was isolated. In contrast, the ratio was lower for cases with salmonella and shigella infection, indicating that most people having these infections present to their general practitioners (Table 3.4). On comparing the results of the reporting system, it was found that cases of non-bacterial gastroenteritis were less likely to be reported to national surveillance. The rate ratio of community cases of gastroenteritis to the cases reaching national surveillance scheme was lower for bacterial pathogens (salmonella 3.2 : 1, campylobacter 7.6 : 1) compared with that of the viruses (rotavirus 35 : 1). [EL = 3]

The UK HPA is a non-departmental public body and its Centre for Infections carries out a range of work on the prevention of infectious disease. The remit of this body includes infectious disease surveillance, and it regularly updates data on enteric pathogens isolated in patients with gastroenteritis. The data are based on submitted laboratory reports, are stratified by regions, age group and year, and although incomplete can identify important trends. Table 3.5 lists the various pathogens identified in the stool samples of children over the period 2002–2006.

Evidence summary

Although results from three hospital-based studies show variation in the proportion of children with gastroenteritis (45%, 75% and 58%) who had pathogenic enteric organisms isolated from their stool examination, rotavirus was detected as the most common cause of gastroenteritis in children in all the studies. Bacterial and protozoal organisms were detected less commonly. Other studies have identified norovirus and adenovirus as other common viral causes, with norovirus being more common than adenovirus. However, rotavirus was identified about four times more often and the results were similar from the community and from hospital settings.

Table 3.4 Incidence of infectious intestinal disease identified in patients from the community and those presenting to general practice¹¹

Infectious agent	Incidence in community per 1000 person-years (95% CI)	Incidence in GP practice per 1000 person-years (95% CI)	Rate ratio of community cases to GP cases (95% CI)
<i>Viruses</i>			
Adenovirus group F	3.0 (1.7–5.4)	0.9 (0.7–1.1)	3.4 (1.8–6.3)
Astrovirus	3.8 (2.3–6.4)	0.9 (0.7–1.1)	4.4 (2.5–7.6)
Calicivirus	2.2 (1.1–4.3)	0.43 (0.27–0.60)	5.1 (2.4–10.7)
Rotavirus group A	7.1 (4.8–10.4)	2.3 (1.8–2.9)	3.1 (2.1–4.6)
Rotavirus group C	0.5 (0.1–2.2)	0.06 (0.02–0.17)	8.9 (1.9–41.3)
Small round structured viruses	12.5 (9.4–16.7)	2.0 (1.4–2.7)	6.3 (4.6–8.6)
<i>Bacteria</i>			
Aeromonas spp.	12.4 (9.4–16.7)	1.9 (1.5–2.4)	6.7 (4.9–9.1)
Bacillus spp.	0	0.05 (0.01–0.15)	–
Campylobacter spp.	8.7 (6.1–12.3)	4.1 (3.3–5.1)	2.1 (1.5–3.0)
<i>Clostridium difficile</i>	1.6 (0.7–3.6)	0.2 (0.1–0.3)	8.0 (3.4–19.3)
<i>Clostridium perfringens</i>	2.4 (1.3–4.7)	1.3 (1.0–1.7)	1.9 (1.0–3.7)
<i>E. coli</i> O157	0	0.03 (0.01–0.11)	–
<i>E. coli</i> non-O157	0.8 (0.3–2.5)	0.06 (0.02–0.17)	13.4 (3.6–49.6)
Salmonella spp.	2.2 (1.1–4.3)	1.6 (1.2–2.1)	1.4 (0.7–2.8)
Shigella spp.	0.3 (0.04–1.9)	0.3 (0.2–0.5)	1.0 (0.1–7.3)
<i>Staphylococcus aureus</i>	0.3 (0.04–1.9)	0.1 (0.05–0.2)	2.5 (0.3–19.0)
Vibrio spp.	0	0.01 (0.001–0.05)	–
Yersinia spp.	6.8 (4.6–10)	0.6 (0.4–0.9)	11.7 (7.5–18.3)
<i>Protozoa</i>			
<i>Cryptosporidium parvum</i>	0.8 (0.3–2.5)	0.43 (0.3–0.6)	1.9 (0.6–6.1)
<i>Giardia lamblia</i>	0.5 (0.1–2.2)	0.3 (0.2–0.5)	1.9 (0.5–7.9)
No organism identified	117 (107–129)	14.8 (12.8–17.2)	7.9 (7.1–8.8)
Total	194 (181–208)	33.1 (29.4–37.5)	5.8 (5.4–6.3)

Table 3.5 Laboratory reports of enteric pathogen isolates, England and Wales (2002–2006) stratified by age; data from the HPA website⁶³

Infesting organism	2002	2003	2004	2005	2006	Cumulative total for 5 year period
Adenovirus ^a						
0–1 month	0	0	0	1	0	1
1–11 months	24	31	17	11	26	109
1–4 years	22	53	18	15	25	133
						Total: 243
Astrovirus	data unavailable					
Bacillus spp.	data unavailable					
<i>Clostridium botulinum</i> ^b	data unavailable					
Calicivirus						
0–1 month	0	0	0	0	0	0
1–11 months	11	13	25	10	2	61
1–4 years	7	15	17	8	6	53
						Total: 114
Campylobacter						
<1 year	879	846	846	746	747	4064
1–4 years	2688	2425	2407	2490	2440	12450
						Total: 16 514
<i>Vibrio cholerae</i>	data unavailable					
Cryptosporidium						
0–1 month	7	6	5	10	4	32
1–11 months	75	163	113	156	125	632
1–4 years	839	1516	991	1205	934	5485
						Total: 6149
<i>E. coli</i> O157	data unavailable ^c					
<i>Entamoeba histolytica</i>						
0–1 month	0	0	0	0	0	0
1–11 months	0	0	0	0	0	0
1–4 years	5	4	1	1	2	13
						Total: 13
<i>Giardia lamblia</i>						
0–1 month	30	34	30	23	37	154
1–11 months	333	375	358	283	315	1664
1–4 years	149	168	136	139	120	712
						Total: 2530
<i>Listeria monocytogenes</i>	data unavailable					
Norovirus						
0–1 month	4	6	8	1	2	21
1–11 months	120	97	91	51	80	439
1–4 years	144	75	121	63	98	501
						Total: 961
Rotavirus	data unavailable					
Salmonella ^d						
<1 year	671	638	547	490	615	2961
1–4 years	1531	1465	1376	1330	1489	7191
						Total: 10 152
Shigella	data unavailable					

^a Adenovirus data includes adenovirus 40, 41, EM and 'Adenovirus F'.

^b One case of childhood botulism in the last 10 years: a 5-month-old female in 2001.

^c *E. coli* O157: no data provided by HPA, but stated, '*E. coli* O157 is a relatively rare cause of infectious gastroenteritis in England and Wales, however, the disease is severe and sometimes fatal, particularly in infants, young children and the elderly.'

^d Salmonella data exclude *S. typhi* amp and *S. paratyphi*.

The most frequent pathogens causing bacterial gastroenteritis reported in the published studies and the HPA website were campylobacter, salmonella and *E. coli*, while cryptosporidium was the most common protozoal infection detected. There were no published population-based data comparing the detection of viral pathogens with bacterial pathogens, but results from the population-based study suggest that cases of non-bacterial gastroenteritis are less likely to be reported to the national surveillance authority than the cases of bacterial gastroenteritis.

Clinical question

Which enteric pathogens are most commonly identified in children returning to the UK with traveller's diarrhoea?

Gastroenteritis is the most commonly reported travel-associated illness in England and Wales. No published data were identified to provide information on this question. Information was again collected from the HPA website,⁶⁴ as given in Table 3.6, but the age-specific data were not available.

Evidence summary

Salmonella was the most commonly reported cause of gastroenteritis associated with overseas travel. The other commonly reported enteric pathogens were campylobacter, shigella and cryptosporidium. While salmonella, campylobacter and cryptosporidium were reported to be associated with travel in Europe, infections with shigella, giardia and entamoeba were associated with travel to the Indian subcontinent and sub-Saharan and southern Africa.

GDG translation from evidence to recommendations

Rotavirus is the predominant single pathogen responsible for gastroenteritis in children. Other viral pathogens, although individually less common, collectively accounted for many other cases. Norovirus has been recognised increasingly as an important cause of gastroenteritis. A range of other viruses, including adenovirus, astrovirus, and calicivirus may also be responsible. Bacterial infections, particularly campylobacter and salmonella species, and protozoal infections such as cryptosporidium may also cause gastroenteritis. In those with a history of recent overseas travel, the likelihood of infection with salmonella, campylobacter, cryptosporidium and other infections unusual in the UK is greater.

The GDG agreed that in, in keeping with current practice, children presenting with acute diarrhoea do not usually require stool microbiological investigation. Most have viral gastroenteritis. Even if the illness is due to a bacterial or protozoal enteric infection, most children do not require antimicrobial treatment (see Chapter 7 on antibiotic therapy), and so identification of a specific pathogen is not generally required.

However, the GDG agreed that in some circumstances microbiological investigation should be considered, as listed below.

- If the clinician is in doubt about the diagnosis of gastroenteritis, isolation of a stool pathogen can provide diagnostic reassurance. Using routine microbiological techniques including stool microscopy, culture and standard viral detection methods, a causative pathogen can be identified in most patients with gastroenteritis.
- It is also important to investigate those who present with bloody and/or mucoid diarrhoea, because this can be due to a range of important and potentially serious disorders.
 - Various non-infective inflammatory bowel disorders may present with bloody stools. Infants (both breastfed and bottle-fed) may present with bloody diarrhoea due to non-specific colitis; this may be an allergic phenomenon, although the aetiology is often uncertain. Inflammatory bowel disease (ulcerative colitis or Crohn's disease) may sometimes begin in early childhood, and the presentation can be acute and associated with bloody diarrhoea. Without evidence of an infective cause, it may be impossible to distinguish between bacterial or amoebic dysentery and a first episode of bloody diarrhoea due to ulcerative colitis or Crohn's colitis.
 - Various surgical disorders, such as intussusception, could also be associated with passage of blood and/or mucus. Although most children with bloody diarrhoea due to an enteric

Table 3.6 Laboratory reports of enteric pathogens isolated from patients with a history of recent travel abroad; data from the HPA website⁶⁴

Region of world	Bacterial pathogens				Protozoal pathogens				Viral
	Campylobacter	Salmonella	Shigella	<i>E. coli</i> O157	Cryptosporidium	Giardia	Entamoeba	Enterovirus	
Europe	716	1454	14	33	337	52	4	12	
Indian subcontinent	233	245	176	2	37	92	12	17	
North Africa and Middle East	170	265	136	17	27	27	6	1	
Southeast Asia and Far East	132	196	44	–	3	19	5	3	
Sub-Saharan and southern Africa	58	157	54	4	11	44	27	–	
Caribbean	26	111	8	–	11	9	–	–	
South and Central America	45	48	41	–	4	16	2	1	
More than one region	5	13	–	–	1	6	2	–	
Other	21	40	8	5	4	4	–	2	
Region unspecified	94	247	5	1	21	31	7	4	
Total	1500	2776	486	62	456	300	65	40	

infection do not require antimicrobial therapy, this is not always so. Treatment is indicated for salmonella gastroenteritis in young infants and in immunocompromised children (see Chapter 7)

- Enteric infection with enterohaemorrhagic *E. coli* (mainly *E. coli* O157:H7) often presents with bloody diarrhoea. These children are at risk of developing HUS, a life-threatening condition. Early microbiological diagnosis is therefore important.
- Rarely, children may present with bloody diarrhoea associated with antibiotic-related pseudomembranous colitis, often due to *C. difficile*. Here *C. difficile* toxin may be detected in the stool.
- It is also reasonable to consider investigating children in whom diarrhoea persists for more than 7 days, because certain treatable enteric infections (for example, giardiasis) may be responsible.
- If a child presenting with acute diarrhoea is very ill and the possibility of septicaemia requires empiric antibiotic therapy, stool microbiological investigation would be indicated. Some patients with bacterial dysentery (salmonella or shigella) may have bacterial septicaemia, and stool culture could identify the responsible pathogen.
- Various pathogens requiring antimicrobial treatment, such as *Giardia lamblia*, shigella and salmonella (in selected cases), are more commonly identified in patients returning from other countries. The GDG therefore agreed that stool microbiological testing should be considered in those with a history of recent overseas travel.

The GDG recognised the importance of providing appropriate and adequate clinical information to the laboratory, including the clinician's suspicion of any unusual pathogen, in order to inform the investigative strategy. Certain organisms require special arrangements for collection or transport to optimise identification. Particular pathogens may sometimes require a targeted approach with specific laboratory techniques.

The GDG recognised that within hospitals and other institutions it may be important to gather data on the specific pathogens responsible for gastroenteritis, but policy on this is outside the scope of this guideline.

The GDG recognised that the public health authorities have access to local and national epidemiological data, and have a central role in the management of outbreaks of gastroenteritis. It is therefore important to discuss with the authority any suspected outbreak of gastroenteritis and its implications.

Recommendations on stool microbiological investigation in diagnosis

Consider performing stool microbiological investigations if:

- the child has recently been abroad *or*
- the diarrhoea has not improved by day 7 *or*
- there is uncertainty about the diagnosis of gastroenteritis.

Perform stool microbiological investigations if:

- you suspect septicaemia *or*
- there is blood and/or mucus in the stool *or*
- the child is immunocompromised.

Notify and act on the advice of the public health authorities if you suspect an outbreak of gastroenteritis.

If stool microbiology is performed:

- collect, store and transport stool specimens as advised by the investigating laboratory
- provide the laboratory with relevant clinical information.

3.2.2 Other laboratory investigations

The GDG examined evidence regarding the potential value of various blood tests in distinguishing bacterial from viral gastroenteritis. As discussed earlier, this might be important for clinical management in some patients.

Clinical question

How accurate are laboratory blood tests in distinguishing bacterial from viral gastroenteritis?

There is variation in practice regarding the use of laboratory blood tests in distinguishing between bacterial and viral causes of gastroenteritis, hence their accuracy in detecting these causes was sought.

Evidence overview

Four diagnostic studies were included in this section, one with EL = 2 and the rest with EL = 3. In the first three studies, the accuracy of acute-phase proteins was evaluated for detecting bacterial gastroenteritis, and C-reactive protein (CRP) was assessed in all the studies, while ESR, interleukin-6 (IL-6) and interleukin-8 (IL-8) were assessed in one study each. The last study evaluated the diagnostic ability of total and differential blood count in differentiating bacterial from viral causes of gastroenteritis.

The first study, from Italy,⁶⁵ looked at the diagnostic accuracy of CRP and ESR measurements in the differentiation of bacterial and viral gastroenteritis. Over a 4 year period, it recruited 111 children aged between 1 and 60 months admitted to a hospital with acute diarrhoea lasting more than 12 hours but less than 15 days. Children with chronic gastrointestinal diseases such as cow's milk protein intolerance, Crohn's disease, gastro-oesophageal reflux or chronic diseases were excluded. After admission, all children had blood taken for the measurement of CRP and ESR levels, while stool culture was performed to detect bacterial aetiology and viruses detected by ELISA testing on the stool specimens. The accuracy of CRP in detecting bacterial or viral gastroenteritis was calculated at the cut-off values of 12, 20 and 35 mg/l, while elevated ESR was taken as value ≥ 25 mm/hour. Of the 111 children, 53 (48%) were diagnosed with bacterial gastroenteritis (mainly non-typhoidal salmonella), 35 (32%) had viral gastroenteritis and the remaining 21% had culture-negative infections. The mean CRP level in children with bacterial infections was significantly higher than in those with viral infections ($P < 0.001$) and culture-negative infections ($P < 0.01$). CRP levels were strongly associated with bacterial infections at all three cut-offs: 12 mg/dl (OR 25.8; 95% CI 7.6 to 87.9), 20 mg/l (OR 46.4; 95% CI 5.9 to 365) and 35 mg/l (OR 27; 95% CI 3.4 to 212). The specificity of CRP in detecting bacterial gastroenteritis was high at all the cut-off levels (89% at 12 mg/l and 97% at both 20 mg/l and 35 mg/l) but the highest sensitivity was 77% at 12 mg/dl, compared with 58% and 44% at the other two cut-off values, respectively. The area under receiver operating characteristic curve (AROC) at 12 mg/l was 0.83. Raised ESR levels (≥ 25 mm/hour) were also strongly associated with bacterial infections (OR 3.5; 95% CI 1.2 to 9.9) and showed a sensitivity of 42%, specificity of 83% and AROC of 0.62 for detecting them. Raised total leucocyte count did not show any statistically significant association with any of the three infections. [EL = 2]

The second study, from Taiwan/China,⁶⁶ aimed to determine whether IL-6, IL-8 and CRP were useful diagnostic markers in differentiating bacterial from viral gastroenteritis. The study included 56 children (mean age 2.5 years) admitted with acute gastroenteritis, of whom 21 had rotavirus (by Rotaclone® test), 18 had bacterial infections (by stool culture with salmonella species isolated predominantly) while 17 children were recruited as controls. Children with chronic disease or history of persistent/intractable diarrhoea were excluded. No details were provided about the control group or exclusion criteria. The concentration of both CRP and IL-6 were significantly higher in children with bacterial gastroenteritis than in those with viral infections ($P < 0.001$) and the control group ($P < 0.001$). IL-8 concentrations were elevated in both bacterial and viral infections and there was no statistically significant difference in the levels between the two groups. Diagnostic accuracy results were analysed using ROC curves and it showed best results for CRP, with the AROC being 0.90 at the cut-off value of 2 mg/dl, followed by IL-6 with an AROC of 0.83 at the cut-off value of 10 pg/ml. At these cut-off values, the sensitivity and specificity of CRP in detecting bacterial gastroenteritis were 83% and 76%, respectively, while those of IL-6 were 78% and 86%, respectively. IL-8 was found to be of less diagnostic value, with an AROC of 0.68, sensitivity of 50% and specificity of 67% at the cut-off value 70 pg/ml. [EL = 3]

In the third study, from Israel,⁶⁷ the ability of the quick-read CRP (QR-CRP) test to detect bacterial gastroenteritis was determined in a convenience sample of 44 children (age range 4 days to 17 years, median age of 2.4 years) admitted to the emergency department of a tertiary hospital. All

children had symptoms of vomiting, diarrhoea more than three episodes and fever and underwent laboratory testing. Exclusion criteria were not defined. Bacterial aetiology was determined by stool culture while antigen testing was used to isolate rotavirus, but it was done in only 28 children. QR-CRP was performed at the bedside with a level of 8 mg/l or more considered as a positive test. Stool culture was positive for bacteria in eight children while rotavirus was isolated in 13 children. The mean CRP concentration was significantly higher in children with bacterial gastroenteritis than in those with viral gastroenteritis ($P < 0.001$). The ROC curve was used to calculate the diagnostic accuracy of QR-CRP. The best cut-off value derived from the ROC curve was 95 mg/l and, at this cut-off value, QR-CRP showed a sensitivity of 87%, specificity of 92% and AROC of 0.94 in detecting bacterial gastroenteritis. [EL = 3]

Another study from Israel⁶⁸ evaluated the ability of total and differential leucocyte counts to differentiate bacterial from non-bacterial gastroenteritis infections. This study recruited 238 children admitted to hospital with gastroenteritis but further details about demographic characteristics were not specified. Bacterial pathogens were isolated by stool culture, along with testing for blood counts but no further details were provided about these tests. One hundred and ninety-two children had bacterial gastroenteritis (shigella in 130, salmonella and campylobacter in 25 each and *E. coli* in 12) while 46 children were in the non-bacterial group. The total white blood counts were similar between the aetiological groups but great variation was observed in the differential blood counts. The absolute band neutrophil count and the ratio of band neutrophils to total neutrophils were significantly higher in the shigella, salmonella and campylobacter groups compared with the *E. coli* and non-bacterial groups ($P < 0.05$ for all comparisons). Among all the bacterial pathogens, children with shigella had the highest values for both these parameters. It was found that band neutrophils to total neutrophils ratio of more than 0.10 could differentiate bacterial infections from *E. coli* and non-bacterial groups with a sensitivity of 84% and a specificity of 75%. [EL = 3]

Evidence summary

There was a lack of good-quality studies to evaluate the ability of laboratory tests to distinguish between bacterial and viral gastroenteritis. Evidence from three studies suggested that raised CRP levels had a high diagnostic ability in detecting bacterial causes, with AROC ranging between 0.83 and 0.94, but the studies used different cut-off values to define a positive CRP test. Other acute-phase proteins (IL-6 and IL-8) and raised ESR levels were found to be less accurate than CRP. The total leucocyte blood count was not helpful in distinguishing bacterial from non-bacterial/viral causes in two studies, while one study reported raised absolute neutrophil band cell count and the ratio of band neutrophils to total neutrophils count (ratio > 0.10) to be useful in distinguishing between the pathogens.

GDG translation from evidence to recommendations

There was evidence that in children with gastroenteritis an elevated CRP would support a diagnosis of bacterial rather than viral gastroenteritis. However, a normal CRP does not exclude the possibility of bacterial gastroenteritis. As discussed elsewhere (Chapter 7 on antibiotic therapy), in the UK most children with bacterial gastroenteritis do not require antibiotic treatment. However, infants younger than 6 months and immunocompromised children should be treated with antibiotics if they have salmonella gastroenteritis. In such vulnerable patients if bacterial gastroenteritis is clinically suspected, antibiotic therapy should be commenced while awaiting the results of stool microbiological investigations. It would not be safe to withhold antibiotic treatment based on a normal CRP result. As measurement of the CRP would rarely influence management, the GDG did not consider that its routine use would be cost-effective.

The GDG considered that, in keeping with normal clinical practice, a blood culture (the gold standard for septicaemia) should be performed prior to commencing antibiotic therapy in children with suspected or confirmed bacterial gastroenteritis.

Children with *E. coli* O157:H7 infection are at risk of developing HUS and the GDG considered that these children should be monitored for the development of microangiopathic haemolytic anaemia, thrombocytopenia and renal insufficiency. This should be done in consultation with an appropriate specialist.

Recommendations on other laboratory investigations in diagnosis

Perform a blood culture if giving antibiotic therapy.

In children with *Escherichia coli* O157:H7 infection, seek specialist advice on monitoring for haemolytic uraemic syndrome.

4 Assessing dehydration and shock

4.1 Clinical assessment

Introduction

Dehydration is the primary serious complication of gastroenteritis. To manage gastroenteritis safely and effectively it is necessary to be able to recognise the presence of dehydration based on clinical assessment. Those with dehydration require fluid administration to replace the fluid and electrolyte deficit. Many have suggested criteria for determining the degree of dehydration in order to try to accurately estimate the deficit replacement to be administered. Some children with gastroenteritis may develop hypovolaemic shock, requiring specific emergency treatment. It is critically important that the manifestations of shock are immediately recognised. In this chapter, these matters are addressed in detail.

Recognising the child with a lesser degree of dehydration is not as easy as identifying the presence of advanced dehydration or hypovolaemic shock. In practice, when assessing a child with gastroenteritis, the clinician should first consider whether there are risk factors for dehydration, i.e., how likely it is that the child is or may soon become dehydrated. Second, the clinician should decide whether there are symptoms and signs present that indicate the presence of dehydration. The GDG therefore considered both of these matters as important elements in the assessment for dehydration.

4.1.1 Risk factors for dehydration

Clinical question

What factors are associated with an increased risk of dehydration?

In total, 40 papers of potential importance were retrieved after the literature search, of which 35 were excluded after being assessed. Thus four case-control studies describing risk factors for the development of dehydration and published in five papers have been included.⁶⁹⁻⁷³ Since all the studies were conducted in developing countries, efforts have been made to describe clinical risk factors relevant to the UK paediatric population.

Evidence overview

The first paper was a case-control study from India⁶⁹ with a study sample of 379 infants with acute gastroenteritis of less than 24 hours' duration. Cases were defined as infants with moderate or severe gastroenteritis ($n = 243$), while controls had no or mild dehydration ($n = 136$). Various factors were evaluated for the risk of dehydration: aetiology, feeding practices, management of diarrhoea, hygiene practices, history of measles and clinical features on admission. Univariate analysis identified various risk factors associated with increased risk. However, after controlling for confounding variables during multivariate analysis, only two factors were found to be significantly associated with an increased risk of dehydration: withdrawal of breastfeeding during diarrhoea (OR 6.8; 95% CI 3.8 to 12.2; $P < 0.001$) and not giving oral rehydration salt (ORS) solution during diarrhoea (OR 2.1; 95% CI 1.2 to 3.6; $P = 0.006$). Age, severity of symptoms and nutritional status were identified as major confounding variables. There was a significant risk of dehydration if the child was younger than 12 months (OR 2.7; 95% CI 1.5 to 5.0; $P = 0.001$), had increased frequency of stool > 8 per day (OR 4.1; 95% CI 2.4 to 7.0; $P < 0.00001$), had increased frequency of vomiting > 2 per day (OR 2.4; 95% CI 1.4 to 4.0; $P = 0.001$) or was severely malnourished with weight for age < 60 th centile according to the Indian Academy of Paediatrics (IAP) classification (OR 3.1; 95% CI 1.6 to 5.9; $P = 0.001$). [EL = 2+]

Children younger than 5 years with acute gastroenteritis (duration not specified) and with either severe or moderate dehydration ($n = 387$ cases) or mild or no dehydration ($n = 387$ controls) and admitted in a hospital were described in another case-control study from India.⁷⁰ The authors investigated risk factors for dehydration in terms of demographic factors, nutritional status, hygiene practices, clinical features on admission, history of measles and management of diarrhoea. Multivariate analysis showed age younger than 12 months (OR 1.5; 95% CI 1.02 to 2.3; $P = 0.038$) and Muslim religion (OR 1.64; 95% CI 1.01 to 2.7; $P = 0.048$) to be associated with risk of dehydration but the lower values of the confidence intervals were close to the null value. Severe undernutrition (weight for age < 60th centile on the IAP classification) was significantly associated with dehydration (OR 1.6; 95% CI 1.3 to 1.9; $P < 0.001$). Clinical features on admission significantly associated with dehydration included increased stool frequency > 8 per day (OR 8.8; 95% CI 5.9 to 13.0; $P < 0.001$) and vomiting frequency > 2 per day (OR 2.6; 95% CI 1.7 to 3.8; $P < 0.001$). History of measles in the past 6 months (OR 2.9; 95% CI 1.5 to 5.6; $P = 0.001$), withdrawal of breastfeeding during diarrhoea (OR 3.6; 95% CI 2.1 to 6.2; $P < 0.001$), withdrawal of fluids during diarrhoea (OR 1.6; 95% CI 1.1 to 2.4; $P < 0.001$) and not giving ORS solution or 'home available fluids' during diarrhoea (OR 1.98; 95% CI 1.3 to 2.9; $P < 0.001$) were all significantly associated with increased risk of dehydration. [EL = 2+]

Results from a third case-control study from Brazil were published in two articles.^{71,72} Cases included children younger than 2 years admitted with diarrhoea of less than 8 days' duration with moderate or severe dehydration ($n = 192$), while controls were children matched to cases by neighbourhood and age who experienced non-dehydrating diarrhoea in the week preceding the study ($n = 192$). Cases and controls were compared using logistic regression analysis of matched studies. The authors looked at a wide range of prognostic factors including biological, anthropometric and dietary variables, morbidity and clinical symptoms.

The first publication⁷¹ reported that, although many factors were associated with an increased risk of dehydration after adjustment for age and socio-economic status, strong association (at $P < 0.001$) was seen only for the child's age, birthweight and other anthropometric measures, birth interval and feeding mode. Younger age was significantly associated with an increased risk of dehydration with the risk about seven times higher in the 2–3 month age group compared with those in the 9–11 month age group (adjusted OR 7.1; 95% CI 3.0 to 16.5). Children of low birthweight (<2500 g) were about three times more likely to become dehydrated than other children. Although other growth-related measures (height for age, weight for age, length of age) showed evidence of significant association, these more complex indices were found to be less useful in terms of sensitivity and specificity. The risk of dehydration was also three times higher in children not breastfed compared with those who received only breast milk (adjusted OR 3.3; 95% CI 1.4 to 7.5). [EL = 2+]

In the second publication,⁷² it was reported that breastfeeding reduced the risk of dehydration when compared with feeding with other types of milk (formula or cow's milk). After adjustment for age and other confounding variables, it was seen that children only on cow's or formula milk had a significantly higher risk of developing dehydration compared with children who were exclusively breastfed (adjusted OR 6.0; 95% CI 1.8 to 19.8 for cow's milk and adjusted OR 6.9; 95% CI 1.4 to 33.3 for formula feeds). There was no difference in the risk of dehydration if children continued with their usual feeds during illness (either breastfeeds or other feeds), but breastfed children who stopped feeding during illness had a statistically significant increase in the risk (adjusted OR 6.4; 95% CI 2.3 to 17.3). It was also observed that the risk of dehydration was greatest during the time period when breastfeeding was stopped, and this higher risk remained statistically significant till after 6 months of full weaning. [EL = 2+]

The fifth paper reported a case-control study conducted in a hospital in Bangladesh⁷³ that included 240 children younger than 2 years with acute gastroenteritis (duration less than 7 days) of which 80 children had severe or moderate dehydration (cases) and 160 children had 'no signs of dehydration' (controls). The cases and controls were matched by age. Thirty-eight socio-demographic, clinical or environmental factors were studied for their influence on development of dehydration. In addition to a number of socio-demographic and environmental factors, there was a statistically significant association (at $P < 0.05$) of the following clinical factors with dehydration: duration of diarrhoea at hospital attendance, stool frequency of more than five per day, 'vomiting during episode', receiving oral rehydration therapy (ORT) at home before

admission, receiving drugs at home before admission and 'wasted child'. All the significant factors were then analysed in a step-wise regression model and the results showed two clinical factors to be independently associated with the development of dehydration: vomiting during episode and received ORT at home before admission. Since the information was collected by a pre-tested questionnaire, information on the preparation and method of giving oral fluids could not be collected and the authors attributed the increased risk in children receiving ORT to ineffective preparation and administration of oral fluids. [EL = 2+]

Evidence summary

There were four relevant case-control studies of good quality [all EL = 2+] conducted in countries with similar healthcare settings but different from that of the UK. Despite the different location of research and culture-specific risk factors investigated, these studies showed consistent results for widely applicable risk factors for the development of dehydration in children with gastroenteritis. In terms of demographic factors, younger children (younger than 12 months, with even higher risk for those very young) and those with malnutrition were at a greater risk of dehydration. The studies showed a consistent and strong association of severity of symptoms, i.e. increased frequency of vomiting (>2 episodes per day) and stool production (>5 episodes per day), with a greater risk of dehydration. In terms of management, withdrawal of breastfeeding and other fluids including ORS solution during diarrhoea were strongly associated with risk of dehydration.

GDG translation from evidence to recommendations

The GDG recognised that the clinical studies available were conducted in resource-poor developing countries. In those settings, there would probably be differences from the UK such as a high prevalence of malnutrition. Nevertheless, the GDG considered that the consistency with which these studies identified specific risk factors was likely to be important. Moreover, some of the findings were both intuitively to be expected and consistent with clinical experience in the UK. Thus, frequent or persistent diarrhoea and vomiting were almost certainly important. The risks identified in relation to age and birthweight were consistent with physiological principles and with clinical experience and were also important. The finding in clinical studies that prior administration of ORT reduced the risk seemed intuitively credible. The consistent finding in the studies that continued breastfeeding was associated with a reduced risk was also potentially important.

Recommendations on risk factors for dehydration

Recognise that the following are at increased risk of dehydration:

- children younger than 1 year, particularly those younger than 6 months
- infants who were of low birthweight
- children who have passed more than five diarrhoeal stools in the previous 24 hours
- children who have vomited more than twice in the previous 24 hours
- children who have not been offered or have not been able to tolerate supplementary fluids before presentation
- infants who have stopped breastfeeding during the illness
- children with signs of malnutrition.

4.1.2 Clinical detection of dehydration and assessment of severity

Clinical questions

What symptoms or signs (individually or in combination) can detect the presence of dehydration?
If dehydration is detected, what symptoms or signs (individually or in combination) can indicate its severity?

It is a common practice in textbooks and guidelines to suggest various clinical manifestations as being indicative of dehydration. It has also been suggested in various published guidelines that the severity of dehydration may be estimated on the basis of symptoms and signs. The GDG explored the published literature to examine the available evidence on these important considerations.

Evidence overview

A systematic literature search was undertaken to inform the two questions. Two studies are included for the first question on the accuracy of clinical signs and symptoms in detecting dehydration, while for the second question four published guidelines are included. These guidelines had employed different methods for classifying severity of dehydration.

Clinical detection of dehydration

Two relevant studies were identified, the first a systematic review of diagnostic studies and the second a cohort study comparing digitally measured capillary refill time (CRT) with conventional CRT and overall clinical assessment.

The systematic review⁷⁴ was conducted to review the precision and accuracy of symptoms, signs and basic laboratory tests for evaluating 5% (or worse) dehydration in young children aged 1 month to 5 years. After a systematic literature search of the MEDLINE database, additional searches were conducted on the individual symptoms and signs, the Cochrane Library, and the reference lists of text books and of all included articles. After reviewing hard copies of 110 articles, 26 articles fulfilled the inclusion criteria and underwent a quality assessment, and 13 studies were finally selected for inclusion.

The reference standard used for assessing dehydration was the 'percentage of volume lost', calculated as the difference between the rehydration weight (the post-rehydration weight) and the acute weight (the weight at presentation) divided by the rehydration weight. Three of the included studies were based on independent, blind comparison of the test with the reference standard but the participants were enrolled in a non-consecutive manner. The remaining ten studies were based on non-independent comparisons of a test with the reference standard and no selection criteria were defined. Hence overall the quality of the included studies was poor. Meta-analysis of the accuracy results using the random effects model was conducted only if more than two studies evaluated a specific diagnostic test. [EL = 3]

Although the authors reported test accuracy results for detecting 5% dehydration, detailed reviewing of the individual studies included in the review revealed that the results were applicable for the detection of 5% or worse dehydration.

Precision

Agreement between parental observation of signs and the signs elicited by trained emergency department nurses was evaluated in a single study. The best level of agreement was reported for sunken anterior fontanelle ($k = 0.73$) and presence of cool extremities ($k = 0.70$), while moderate agreement was seen for general appearance, presence of sunken eyes, absence of tears, and presence of dry mouth (k values in the range 0.46–0.57). Three studies reported on agreement among clinicians but wide variation was seen in the results for the various signs. Prolonged CRT had k values ranging from 0.01 to 0.65, while absent tears had values from 0.12 to 0.75. For the rest of the signs, the level of agreement was either slightly better than the chance agreement (k value in the range 0.50–0.60) or worse than the chance agreement ($k < 0.50$).

Clinical history including symptoms

Three studies were included and all of them evaluated history of low urine output as a test for detecting dehydration. A pooled analysis showed that it did not increase the likelihood of detecting 5% dehydration (+LR 1.3; 95% CI 0.9 to 1.9). However, results from two studies showed that parental reporting of a normal urine output decreased the likelihood of detecting dehydration, although the results were statistically not significant in one study (–LR 0.27; 95% CI 0.14 to 0.51 and –LR 0.16; 95% CI 0.01 to 2.53). One study reported LRs for a number of symptoms, including history of vomiting and diarrhoea (severity), decreased oral intake, and a previous trial of clear liquids, but none of these were found to be helpful in increasing or decreasing the likelihood. This study also suggested that children who had not been previously evaluated by a physician during the illness might be less likely to be dehydrated, but the results were again statistically not significant (–LR 0.09; 95% CI 0.01 to 1.37).

Signs

The results of the test characteristics of various signs are given in Table 4.1. Three signs showed evidence of increasing the likelihood of detecting 5% dehydration: prolonged CRT (four studies,

+LR 4.1; 95% CI 1.7 to 9.8), abnormal skin turgor (four studies, +LR 2.5; 95% CI 1.5 to 4.2) and abnormal respiratory pattern (four studies, +LR 2.0; 95% CI 1.5 to 2.7). Sunken eyes and dry mucous membranes showed a small increase in the likelihood of dehydration (+LR for both 1.7) and the lower limit of their 95% CI was close to the null value. Results for weak pulse as a predictor for dehydration were variable, with one study showing it to be a fair predictor (+LR 3.1; 95% CI 1.8 to 5.4) while another did not (+LR 7.2; 95% CI 0.4 to 150). The presence of cool extremities as a test for dehydration was examined in two studies and both reported imprecise point estimates for the +LR (95% CI too wide to draw conclusions). The 95% CI for the positive and negative LRs for increased heart rate, sunken fontanelle in young infants, and an overall poor appearance included the null value.

A second prospective cohort study⁷⁵ aimed to determine whether CRT measured using a digital device (DCRT) could determine the presence of significant dehydration. The study population comprised 83 children (aged 1 month to 5 years) with acute gastroenteritis admitted to an accident and emergency department in Canada. Following admission and enrolment, the degree of dehydration was estimated using a seven-point Likert scale, CRT was clinically assessed in the conventional way by the paediatric medical staff, and DCRT measured using a small digital video camera with customised graphics software. The reference standard (degree of dehydration) was calculated by measuring the difference between the pre- and post-rehydration weight of the child.

Thirteen (16%) children met the WHO definition of dehydration ($\geq 5\%$), with 12 estimated to have a fluid deficit between 5% and 8% and one with 11% deficit. For these children, there was a strong correlation between the child's fluid deficit and the DCRT (Pearson's correlation coefficient 0.75; $P < 0.001$). The AROC for detecting presence of dehydration $\geq 5\%$ was 0.99 for DCRT and 0.88 for clinical assessment. DCRT showed the best result for predicting dehydration more than 5%, with 100% sensitivity, 91% specificity and a +LR of 11.4 (95% CI 5.4 to 22). Compared with the clinical assessment scale, conventional CRT showed better results for specificity (88% versus 81%) and for +LR (4.5 versus 4.1), but poorer results for sensitivity (54% versus 77%). [EL = 2]

Clinical assessment of the severity of dehydration

Four guidelines had classified degrees of dehydration by using a combination of signs and symptoms. These are summarised in Tables 4.2–4.4.

Evidence summary

Results from a systematic review [EL = III] suggest that prolonged capillary refill time, abnormal skin turgor and abnormal respiratory pattern are the signs most useful to detect 5% or worse dehydration in a child with gastroenteritis. Sunken eyes and dry mucous membrane were also found to be useful although their predictive value was less than the above three signs. For the other signs and symptoms, either the pooled likelihood ratios were statistically not significant or there was wide variation in the results from individual studies. Results also show that there was generally a poor agreement between clinicians on the presence of these clinical signs. Another study [EL = II] showed that CRT measured using a digital video technique (DCRT) had better accuracy in detecting dehydration of 5% or worse than the conventional clinical CRT and the clinical assessment scale.

Although the published guidelines employed different methods of classifying the severity of dehydration, they all used similar symptoms and signs (individually or in combination) for these classification methods.

GDG translation from evidence to recommendations

Clinical detection of dehydration

A range of symptoms and signs have traditionally been considered useful in the detection of dehydration. The GDG found that many of these did not have evidence with regard to their reliability, particularly in those children with less severe degrees of dehydration.

The GDG considered that the identification of symptoms useful for the detection of dehydration would be important, particularly because they could be employed as part of the remote assessment process. However, the only symptom of possible value identified from the evidence was a report of 'normal urine output' and the evidence between studies was inconsistent. The GDG considered that enquiry should be made about this matter, and that some reassurance

Table 4.1 Summary characteristics of clinical signs used to detect 5% dehydration

Finding (no. of studies)	Total no. of children	Summary likelihood ratios (with 95% CI)		Sensitivity (95% CI)	Specificity (95% CI)
		Positive (+LR)	Negative (-LR)		
Prolonged capillary refill (4)	478	4.1 (1.7 to 9.8)	0.57 (0.39 to 0.82)	0.60 (0.29 to 0.91)	0.85 (0.72 to 0.98)
Abnormal skin turgor (5)	602	2.5 (1.5 to 4.2)	0.66 (0.57 to 0.75)	0.58 (0.40 to 0.75)	0.76 (0.59 to 0.93)
Abnormal respiratory pattern (4)	581	2.0 (1.5 to 2.7)	0.76 (0.62 to 0.88)	0.43 (0.31 to 0.55)	0.79 (0.72 to 0.86)
Sunken eyes (4)	533	1.7 (1.1 to 2.5)	0.49 (0.38 to 0.63)	0.75 (0.62 to 0.88)	0.52 (0.22 to 0.81)
Dry mucous membranes (4)	533	1.7 (1.1 to 2.6)	0.41 (0.21 to 0.79)	0.86 (0.80 to 0.92)	0.44 (0.13 to 0.74)
Cool extremity (2) ^a	206	1.5, 18.8	0.89, 0.97	0.10, 0.11	0.93, 1.00
Weak pulse (2) ^a	360	3.1, 7.2	0.66, 0.96	0.04, 0.25	0.86, 1.00
Absent tears (3)	398	2.3 (0.9 to 5.8)	0.54 (0.26 to 1.13)	0.63 (0.42 to 0.84)	0.68 (0.43 to 0.94)
Increased heart rate (3)	462	1.3 (0.8 to 2.0)	0.82 (0.64 to 1.05)	0.52 (0.44 to 0.60)	0.58 (0.33 to 0.82)
Sunken fontanelle (3)	308	0.9 (0.6 to 1.3)	1.12 (0.82 to 1.54)	0.49 (0.37 to 0.60)	0.54 (0.22 to 0.87)
Poor overall appearance (3)	398	1.9 (0.97 to 3.8)	0.46 (0.34 to 0.61)	0.80 (0.57 to 1.00)	0.45 (-0.1 to 1.00)

^a Point estimate from individual studies.

Table 4.2 Classification of dehydration severity by Armon *et al.*¹⁷

No dehydration	Mild–moderate dehydration	Severe dehydration
Less than 3% weight loss	3–8% weight loss	≥9% weight loss
No signs	Ordered by increasing severity: <ul style="list-style-type: none"> • dry mucous membranes (be wary in the mouth breather) • sunken eyes (and minimal or no tears) • diminished skin turgor (pinch test 1–2 seconds) • altered neurological status (drowsiness, irritability) • deep (acidotic) breathing 	Increasingly marked signs from the mild–moderate group plus: <ul style="list-style-type: none"> • decreased peripheral perfusion (cool/mottled/pale peripheries; capillary refill time > 2 seconds) • circulatory collapse

Table 4.3 Classification of dehydration severity by WHO⁷⁶

No dehydration	Some dehydration	Severe dehydration
Not enough signs to classify as some or severe dehydration	Two or more of the following signs: <ul style="list-style-type: none"> • restlessness, irritability • sunken eyes • drinks eagerly, thirsty • skin pinch goes back slowly 	Two or more of the following signs: <ul style="list-style-type: none"> • lethargy/unconsciousness • sunken eyes • unable to drink or drinks poorly • skin pinch goes back very slowly (≥2 seconds)

Table 4.4 Classification of dehydration severity by ESPGHAN⁷⁷

Variable	No signs of dehydration	Some dehydration	Severe dehydration
General condition	Well, alert, restless, irritable	Restless, irritable	Lethargic or unconscious, floppy
Eyes	Normal	Sunken	Very sunken and dry
Tears	Present	Absent	Absent
Mouth/tongue	Moist	Dry	Very dry
Thirst	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly or not able to drink
Skin	Pinch retracts immediately	Pinch retracts slowly	Pinch retracts very slowly
% body weight loss	<5%	5–10%	>10%

could be taken if the urine output was said to be normal. The GDG also agreed that carers were acutely aware of any change in the child's behaviour (irritability, lethargy) and appearance (for example 'sunken eyes'), and so it seemed appropriate to specifically enquire about these.

With regard to the role of physical signs in the detection of dehydration, the GDG examined the evidence from the systematic review and identified two limitations to the included studies. First, the review appeared to report on children with 5% dehydration *or worse* and, given the symptoms and signs identified, the GDG strongly suspected that many of the patients might have been considerably more than 5% dehydrated. Therefore, the stronger associations reported for CRT, abnormal skin turgor and abnormal breathing pattern did not mean that these signs would be useful for the detection of less severe dehydration. On the contrary, the GDG considered that those signs suggested the presence of relatively severe dehydration. Second, neither the prevalence of dehydration nor the post-test probabilities of dehydration were presented. One or other of these parameters was needed to interpret the likelihood ratios presented.

Therefore, this study did not provide reliable evidence on the value of symptoms and signs for the detection of lesser degrees of dehydration. However, the GDG agreed that the presence of one or more symptoms or signs evaluated in those studies and conventionally employed in assessment for dehydration would suggest clinically significant dehydration.

The study of CRT using a digital technique (DCRT) showed a relationship between abnormal DCRT and dehydration. However, this remains an experimental technique that is not yet established as a method for routine clinical use.

Clinical assessment of dehydration severity

The GDG recognised that there was a lack of compelling evidence to support efforts to accurately distinguish varying degrees of dehydration on the basis of symptoms and signs. In the absence of such evidence, any system of classification was inevitably arbitrary and subjective and based on the clinician's judgement and a 'global assessment' of the child's condition.

In the past, it was common to describe three levels of dehydration, referred to as mild (3–5%), moderate (6–9%) and severe ($\geq 10\%$), with an implication that it was possible to make such distinctions based on the clinical assessment (see Table 4.5). A number of recent guidelines (Tables 4.3 and 4.4) had adopted simpler schemes in which just two degrees of dehydration were to be distinguished – 'some dehydration' (or 'mild to moderate dehydration'), variably defined as 3–8% or 5–10% dehydration, and 'severe dehydration', variably defined as $\geq 9\%$ or $>10\%$ dehydration. Even these simpler classifications could be difficult to implement in clinical practice. The GDG considered that it was not possible to accurately distinguish 'sunken' and 'very sunken' or 'deeply sunken' eyes, or between skin pinch retracting 'slowly' and 'very slowly', or between 'dry' and 'very dry' mucous membranes. There was also no evidence on the reliability of these various signs either individually or in combination in distinguishing varying degrees of dehydration. In addition, there was no evidence to justify arbitrary categorisation on the basis of specific numbers of clinical symptoms or signs as had been suggested (Table 4.3).

The GDG decided to adopt a new and even simpler clinical assessment scheme (Table 4.6) Patients would merely be classified as follows: 'no clinically detectable dehydration', 'clinical dehydration' and 'clinical shock'. With this assessment scheme the clinician would have to recognise the presence of clinical dehydration. This simplified scheme does not imply that the degree of dehydration is uniform, but rather acknowledges the difficulties in accurately assessing dehydration severity. The GDG recognised that experienced clinicians could distinguish marked differences in the severity of dehydration. They also considered that clinical signs were likely to be more pronounced and numerous in those with severe dehydration. However, firm recommendations linking clinical symptoms and signs with specific varying levels of dehydration were impossible. The crucial point however, is that the scheme is all that is required to guide fluid management (Chapter 5). In this guideline a standard fluid regimen is recommended for all (non-shocked) children with dehydration, with adjustments being made to the fluid regimen over time based on regular reassessment during the rehydration process.

The GDG was aware of the crucial importance of identifying those children with hypovolaemic shock. They would require specific emergency management with administration of IV fluid boluses (Section 5.4) and so it was essential that signs of shock should be recognised without delay. Many patients with hypovolaemic shock were likely to have obvious and pronounced

Table 4.5 Classification of dehydration severity by the American Subcommittee on Acute Gastroenteritis⁵

Variable	Mild, 3–5%	Moderate, 6–9%	Severe, ≥10%
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal or slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased
Skin turgor	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 per hour	<< 1 ml/kg per hour
Thirst	Slightly increased	Moderately increased	Very thirsty or too lethargic to indicate

signs of dehydration in addition to the specific clinical manifestations of shock. However, this might not always be the case. For example, a small infant with gastroenteritis might experience sudden severe fluid loss at the onset of gastroenteritis sufficient to cause hypovolaemic shock before any signs of dehydration (for example, dry mucous membranes or reduced skin turgor) were present. Hence it was appropriate to distinguish the symptoms and signs of shock from those of dehydration. Inevitably, there was some overlap, in that both dehydration and shock might be associated with a change in conscious state. In dehydration, lethargy or irritability might commonly occur, while in shock there might be a more profound depression of consciousness. Likewise, dehydration would often cause an increased heart rate but in shock this might be much more pronounced. The diagnosis of shock would be based on the clinician's global assessment, taking account of each of the relevant symptoms and signs. With severe shock the manifestations would be unequivocal. In lesser degrees of shock, for example as the symptoms and signs first appeared, there might be some difficulty in distinguishing it from severe dehydration. The GDG concluded that when there was uncertainty the safe approach would be to treat as though shock was present (Section 5.4).

The GDG identified several 'red flag' signs in dehydration whose presence should alert the clinician to a risk of progression to shock (see Table 4.6). These were altered responsiveness (for example, irritable, lethargic), sunken eyes, tachycardia, tachypnoea, and reduced skin turgor. Children with such red flag signs require especially careful consideration and close monitoring. The GDG considered that monitoring to follow the 'illness trajectory' was critically important particularly in these ill children. Thus tachycardia (a red flag sign) would be of even greater concern if it worsened over time, pointing to a serious risk of clinical deterioration and shock.

The GDG recognised that this recommended clinical assessment scheme was novel and would be unfamiliar to clinicians. However, it had the great advantage of simplicity, would be easy to implement, and would provide the clinical information necessary for appropriate fluid management. As discussed later in Chapter 5, those with dehydration will usually be treated with oral fluid rehydration, those with red flag symptoms and/or evidence of deterioration will require careful management, probably in a hospital setting, while those with suspected or definite shock will require emergency IVT in hospital. In the community setting, it will be necessary for the healthcare professional to decide whether monitoring the response to rehydration therapy can be carried out safely in the home setting and if so under what level of supervision (general practitioner, community children's nurse, etc.). Where there are concerns about a parent's ability to monitor their child's condition and to provide appropriate care, referral to hospital might be required.

The GDG considered that recognition of the symptoms and signs of dehydration and shock needs considerable expertise. Clinicians therefore require training and experience in order to ensure competence in assessing children with gastroenteritis. This should be at an appropriate level to allow the individual to work safely and effectively in their specific clinical role.

Recommendation on clinical detection of dehydration and assessment of severity

During remote or face-to-face assessment ask whether the child:

- appears unwell
- has altered responsiveness, for example is irritable or lethargic
- has decreased urine output
- has pale or mottled skin
- has cold extremities.

Use Table 4.6 to detect clinical dehydration and shock.

Table 4.6 Symptoms and signs of clinical dehydration and shock

Interpret symptoms and signs taking risk factors for dehydration into account. Within the category of ‘clinical dehydration’ there is a spectrum of severity indicated by increasingly numerous and more pronounced symptoms and signs. For clinical shock, one or more of the symptoms and/or signs listed would be expected to be present. Dashes (–) indicate that these clinical features do not specifically indicate shock. Symptoms and signs with red flags (🚩) may help to identify children at increased risk of progression to shock. If in doubt, manage as if there are symptoms and/or signs with red flags.

Increasing severity of dehydration →			
	No clinically detectable dehydration	Clinical dehydration	Clinical shock
Symptoms (remote and face-to-face assessments)	Appears well	🚩 Appears to be unwell or deteriorating	–
	Alert and responsive	🚩 Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
	Normal urine output	Decreased urine output	–
	Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
	Warm extremities	Warm extremities	Cold extremities
Signs (face-to-face assessments)	Alert and responsive	🚩 Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
	Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
	Warm extremities	Warm extremities	Cold extremities
	Eyes not sunken	🚩 Sunken eyes	–
	Moist mucous membranes (except after a drink)	Dry mucous membranes (except for ‘mouth breather’)	–
	Normal heart rate	🚩 Tachycardia	Tachycardia
	Normal breathing pattern	🚩 Tachypnoea	Tachypnoea
	Normal peripheral pulses	Normal peripheral pulses	Weak peripheral pulses
	Normal capillary refill time	Normal capillary refill time	Prolonged capillary refill time
	Normal skin turgor	🚩 Reduced skin turgor	–
	Normal blood pressure	Normal blood pressure	Hypotension (decompensated shock)

Research recommendation

In children with gastroenteritis, what is the predictive value of clinical symptoms and signs in assessing the severity of dehydration, using post-rehydration weight gain as the reference standard, in primary and secondary care settings?

Why this is important

Evidence from a systematic review* suggests that some symptoms and signs (for example, prolonged capillary refill time, abnormal skin turgor and abnormal respiratory pattern) are

* Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? *JAMA: the Journal of the American Medical Association* 2004;291(22):2746–54.

associated with dehydration, measured using the accepted 'gold standard' of the difference between pre-hydration and post-hydration weight. However, 10 of the 13 included studies were not blinded and had ill-defined selection criteria. Moreover, all these studies were conducted in secondary care where children with more severe dehydration are managed.

Most children with gastroenteritis can and should be managed in the community* but there is a lack of evidence to help primary care healthcare professionals correctly identify children with more severe dehydration. Symptoms and signs that researchers may wish to investigate include overall appearance, irritability/lethargy, urine output, sunken eyes, absence of tears, changes in skin colour or warmth of extremities, dry mucous membranes, depressed fontanelle, heart rate, respiratory rate and effort, character of peripheral pulses, capillary refill time, skin turgor and blood pressure.

Clinical question

What symptoms and/or signs suggest the presence of hypernatraemic dehydration?

Hypernatraemic dehydration may be defined as dehydration associated with a plasma sodium concentration greater than 150 mmol/l. Some textbooks suggest that the presenting symptoms and signs associated with this condition differ from those in dehydration without hypernatraemia. It is said that these patients may have 'doughy' skin, and tachypnoea, and that many of the signs normally associated with dehydration (reduced skin turgor, dryness of the mucous membranes, skin mottling, sunken eyes, altered vital signs) may not occur. The evidence for these reported differences was sought.

Evidence overview

Only one study was found that reported signs and symptoms associated with hypernatraemic dehydration. A prospective comparative study was conducted in South Africa⁷⁸ to determine the incidence of hypernatraemia in children with diarrhoea and to define its distinguishing symptoms and signs. Serum sodium levels were determined in all children admitted with diarrhoea at the hospital over the course of 1 year ($n = 3889$). In total, 147 (3.8%) were found to be hypernatraemic (serum sodium > 150 mmol/l). A group of 50 consecutive children with an initial serum sodium < 150 mmol/l formed the control group. No inclusion and exclusion criteria were reported. The study participants underwent a full clinical examination and the degree of dehydration was categorised as 'not dehydrated', '5% dehydrated' or '10% dehydrated'. The percentage dehydration was calculated from the difference between the weight on admission and after rehydration.

A significantly greater proportion of those with hypernatraemia were younger than 6 months ($P < 0.01$) compared with the control group. There were no differences regarding gender or nutritional status. Symptoms of central nervous system dysfunction were more common in the hypernatraemic group compared with the non-hypernatraemic children (38% versus 4%; $P < 0.001$). The authors also reported the numbers of children presenting with various central nervous system symptoms for the two groups: 32 versus 2 were drowsy but rousable; 15 versus 0 were jittery, hypertonic or hyperreflexic; 9 versus 0 children were in coma or had convulsions. When clinical estimation of dehydration was compared with the actual degree of dehydration (based on weight change), dehydration was underestimated in 72.5% of the hypernatraemic group compared with 36% of the non-hypernatraemic group ($P < 0.001$). The authors reported that in the hypernatraemic group dehydration was often grossly underestimated. [EL = 2]

Evidence summary

Evidence from a single prospective study indicated that hypernatraemia was more common in young infants (< 6 months) with diarrhoea. Children with hypernatraemic dehydration had an increased frequency of symptoms of central nervous system dysfunction. Using clinical assessment, the severity of dehydration was more often underestimated in hypernatraemic dehydration than in children with dehydration associated with a normal plasma sodium concentration.

* Hay AD, Heron J, Ness A; the ALSPAC study team. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. *Family Practice* 2005;22(4):367-74.

GDG translation from evidence to recommendation

The GDG noted that there was a lack of evidence on this topic. No evidence was found for the often described phenomenon of 'doughy skin', and so it was concluded that this finding could not be relied on to clinically identify patients with hypernatraemic dehydration. The GDG also noted that in some publications from North America the term 'doughy skin' was used with a different meaning – seemingly being synonymous with 'reduced skin turgor', a sign of dehydration more generally. Therefore GDG consensus was that the term 'doughy' was not helpful and hence it has not been used in this guideline. On the other hand, it was the experience of GDG members that hypernatraemic dehydration is associated with neurological signs such as an altered level of consciousness, 'jitteriness' or muscle hypertonicity, and the presence of these signs should prompt laboratory investigation.

Recommendation on assessment of hypernatraemic dehydration

Suspect hypernatraemic dehydration if there are any of the following:

- jittery movements
- increased muscle tone
- hyperreflexia
- convulsions
- drowsiness or coma.

4.2 Laboratory investigations for assessing dehydration

Introduction

There are potential biochemical complications associated with gastroenteritis that can only be identified through blood testing. For example, electrolyte disturbances such as hypernatraemia and hyponatraemia may occur. Hypoglycaemia may occur in some cases. Children with gastroenteritis may become acidotic. Dehydration may lead to pre-renal failure or even acute renal failure. To suggest that all children with gastroenteritis should undergo blood testing would be inappropriate, and yet the clinician must consider the possibility that in some cases clinically important biochemical abnormalities may occur that could require specific treatment. Evidence was therefore sought on the incidence of such biochemical disturbances in children presenting with gastroenteritis, and their accuracy in detecting severity of dehydration. An attempt was made to determine whether the incidence of such complications was increased in specific and clinically identifiable categories of patient.

Clinical questions

How common are biochemical abnormalities in children with gastroenteritis and dehydration?
How accurate are laboratory tests in detecting varying degrees of dehydration?

Evidence overview

After the primary screening, 40 papers were retrieved for reviewing. Most of the retrieved studies had been published in the 1980s and 1990s, used a non-comparative study design and did not give adequate data to calculate the incidences. In the end, five studies were included to provide data on the incidence of biochemical disturbances in children with acute gastroenteritis. For the second part of the question relating to diagnostic accuracy, two studies were included – a systematic review of diagnostic studies and a prospective diagnostic study.

Incidence of biochemical abnormalities

There were three prospective cross-sectional studies from the UK,^{53,57,58} one from Turkey⁷⁹ and one retrospective case series from the USA.⁸⁰ All three studies from the UK have already been included previously under Section 3.2.1.

The first UK study⁵³ included 1148 children younger than 16 years admitted to a sub-regional infectious disease hospital with a diagnosis of gastroenteritis over a 1 year period. Of the admitted children, 55% (635/1148) were younger than 1 year while 5% were over 5 years of age.

Admissions were predominantly from socially disadvantaged families (62% from social classes IV and V). At the time of admission, 8.8% of children (101/1148) were clinically dehydrated, with 1% assessed to have greater than 5% dehydration. The group of dehydrated children ($n = 101$) showed a higher incidence of biochemical disturbances compared with those who were not dehydrated ($n = 1047$): hypernatraemia (sodium levels > 145 mmol/l) 10.9% versus 0.6%, uraemia (urea > 7 mmol/l) 30% versus 5.3% and low bicarbonate levels (< 21 mmol/l) 72% versus 55%. The difference in the incidence of biochemical abnormalities between the two groups was statistically significant ($P < 0.001$) for all the three parameters. [EL = 3]

In the second UK study,⁵⁷ 447 children younger than 2 years and admitted to a hospital with gastroenteritis were recruited over a 1 year period. Seventy-four percent of the children were younger than 1 year and two-thirds of under-1-year-olds were younger than 6 months. The overall incidence of moderate to severe dehydration (assessed clinically) was 14%. Hypernatraemia (sodium levels ≥ 150 mmol/l) occurred in 0.8% of cases, 8% had raised urea concentration (> 6 mmol/l), and 3% had bicarbonate concentration ≤ 15 mmol/l. However, it was not specified whether biochemical abnormalities were found only in children with moderate to severe dehydration. [EL = 3]

Another UK study⁵⁸ included 215 children admitted to four paediatric units in south Wales with gastroenteritis over a 1 year period. The age of the study population ranged from 2 weeks to 9 years and 61% of children were younger than 1 year. The primary aim of the study was to describe the clinical characteristics, incidence of complications, and management (pre-admission and hospital) of the patients. The authors did not specify the total number of cases with clinical dehydration, but overall only 7% were judged to be severely dehydrated. At the time of admission, blood testing was carried out in 35% of children (76/215) on clinical grounds. The incidence of hypernatraemia among all the children (sodium levels > 145 mmol/l) was 0.9%, while 7.9% each had hyponatraemia (sodium < 135 mmol/l) and raised urea concentration (> 6 mmol/l). About 6% of children had acidosis with bicarbonate levels < 15 mmol/l. [EL = 3]

The study from Turkey⁷⁹ aimed to investigate the relationship between blood glucose and serum electrolytes since it was hypothesised that changes in blood glucose levels during diarrhoea complicate the course of the illness, especially when it is associated with electrolyte abnormalities. The study population included 119 children (age range 2 months to 15 years) with gastroenteritis and moderate to severe dehydration (according to WHO criteria) admitted to a tertiary children's hospital over a 3 month period. In order to reduce age-dependant variability of laboratory findings, the study population was further divided into two groups: younger than 2 years and more than 2 years of age. More than half of the study population had body weight/age ratio less than the 10th percentile. Blood samples were drawn at the time of admission in all children. Hypernatraemia (sodium levels > 150 mmol/l) was present in 7.6% of all cases and hyponatraemia (sodium levels < 130 mmol/l) in 3.4%, while 48% of children had bicarbonate levels < 15 mmol/l. Potassium levels < 3 mmol/l were noted in 4.2% of children. Hyperglycaemia (blood glucose levels > 140 mg/dl) was observed in 10.9% of cases while hypoglycaemia (threshold value not defined) was noted in only one child. The mean sodium levels were significantly higher in the hyperglycaemic group of children compared with the rest of children, but there was no difference between the two groups regarding serum bicarbonate levels. Similarly, mean sodium levels were noted to be higher in children younger than 2 years with bicarbonate levels < 15 mmol/l compared with those with higher bicarbonate levels (> 15 mmol/l). A positive correlation was found between blood glucose and serum sodium levels in children younger than 2 years with bicarbonate levels < 15 mmol/l ($r = 0.35$; $P < 0.05$), and this correlation became stronger when the analysis was limited to children with bicarbonate levels < 10 mmol/l ($r = 0.73$; $P < 0.05$). No relationship was observed between blood glucose and serum sodium levels in the older age group. However, the authors did not give detailed information about the correlation data. [EL = 3]

A retrospective case series from the USA⁸⁰ aimed to estimate the prevalence of hypoglycaemia among children with dehydration due to acute gastroenteritis who presented to an urban hospital emergency department. For this study, dehydration was considered to be present in children who received an IV fluid bolus. Hypoglycaemia was defined as serum glucose concentration < 60 mg/dl (3.3 mmol/l). Medical records of 196 children (younger than 5 years) admitted over a 1 year period were reviewed and the mean age of the study sample was 23 months

(SD 14 months). Overall, 9.4% of children (18/192) were found to be hypoglycaemic but only one child had serum glucose levels < 40 mg/dl (2.2 mmol/l). On comparing the characteristics of the hypoglycaemic group of children ($n = 18$) with the non-hypoglycaemic group ($n = 178$), the mean duration of vomiting (\pm SD) was found to be significantly longer in hypoglycaemic children (3.3 ± 1.7 days versus 2.4 ± 2.6 days; $P < 0.05$). Of those children with hypoglycaemia and dehydration, 94% had bicarbonate levels < 18 mEq/l and 19% had blood urea nitrogen (BUN) levels > 18 mg/dl, while in the group of children having normal glucose levels and dehydration, 92% had bicarbonate levels < 18 mEq/l and 29% had BUN levels > 18 mg/dl. The difference between the two groups was not statistically significant for these two parameters. [EL = 3]

The incidences of various biochemical disturbances as identified in the above five studies are shown in Table 4.7. It is important to note that the investigators arbitrarily employed varying definitions for biochemical abnormality, and the clinical importance of these disturbances should be taken into account when considering the results from these studies.

Accuracy of laboratory tests in detecting dehydration

Two studies were included that evaluated the diagnostic accuracy of laboratory investigations for assessing dehydration – a systematic review and a prospective cohort study. The methodology of the systematic review⁷⁴ and the results on the accuracy of signs and symptoms are described in detail under Section 4.1. In this section, only the findings relevant to accuracy of laboratory tests are given.

In the systematic review,⁷⁴ six studies were identified that evaluated the ability of laboratory tests to assess dehydration. Five studies evaluated BUN levels or BUN/serum creatinine ratio as a test for dehydration but they used different thresholds to define an increased level. With a cut-off value of 8, 18 and 27 mg/dl for a high BUN level, the +LRs ranged from 1.4 to 2.9, while a single study found urea levels > 40 mg/dl to significantly increase the likelihood of at least 5% dehydration (+LR 46; 95% CI 2.9 to 733). However, this study had a small sample population and the confidence limits of the likelihood ratio were wide. Acidosis was evaluated in four studies but these studies also used different cut-off values. Two studies defined acidosis as base deficit > 7 mEq/l and they reported +LR of 1.4 and 1.8, and –LR of 0.4 and 0.7, respectively. The other two studies used serum bicarbonate levels < 15 and < 17 mEq/l as indicative of acidosis. Both the studies reported that bicarbonate levels lower than the cut-off values were not helpful in increasing the likelihood of dehydration (+LR of 1.5 and 3.5, respectively), but higher levels were found to be useful in decreasing the likelihood of dehydration (–LR of 0.18 and 0.22, respectively). One study evaluated elevated serum uric acid levels (>600 mmol/l) and increased anion gap (>20 mmol/l) as tests for dehydration but their likelihood ratios contained the null value. [EL = 3]

The second diagnostic study from the USA⁸¹ evaluated the accuracy of urine specific gravity, urine ketone levels and urine output in detecting dehydration. This study was part of a larger study to compare the safety and efficacy of rapid IVT given over 1 hour with that of infusion over 3 hours. The study population included 75 children aged 3–36 months admitted to the emergency department with moderate dehydration (clinically estimated) and requiring IVT due to failure of ORT (refusal, recurrent emesis or inadequate intake). After admission, urine samples were collected by catheterisation or spontaneous void and, following successful rehydration with IVT, repeat samples were collected. The reference standard for estimating the degree of dehydration was the percentage weight loss calculated by dividing the difference between the initial weight and final rehydrated weight with the rehydrated weight. Two-thirds of the children (50/75) had $\geq 3\%$ dehydration while 21% had $\geq 5\%$ dehydration confirmed by the weight-based criterion. No statistically significant correlation was found between urine specific gravity or urine ketone levels with the degree of dehydration. For urine specific gravity, there was no statistically significant increase in the likelihood of either 3% or 5% dehydration at any of the cut-off values (with the 95% confidence limits containing the null value of 1). Similar results were seen for urine ketone levels. Finally, urine output measured after admission and during rehydration therapy did not correlate with the degree of dehydration, and it was not helpful in increasing or decreasing the likelihood of dehydration. [EL = 3]

Table 4.7 Incidence of biochemical disturbances in children with gastroenteritis

Study reference	Number and age of children	Proportion of children with dehydration	Proportion of children with hypernatraemia	Proportion of children with hyponatraemia	Proportion of children with hypokalaemia	Proportion of children with urea concentration > normal	Proportion of children with serum bicarbonate concentration < normal	Proportion of children with elevated glucose
Conway <i>et al.</i> ⁵³	<i>n</i> = 1148 Age range 0–10 years (37% were < 6 months and 82% were < 2 years)	In total, 101/1148 (9%) were dehydrated, of which: • 89/1148 (8%) were <5% dehydrated • 11/1148 (1%) were 5–10% dehydrated • 1/1148 was >10% dehydrated	8/1119 (0.71%) as plasma sodium concentration of ≥150 mmol/l	N/A	N/A	10/101 (30%) of dehydrated children and 56/1047 (5%) children without dehydration had a raised urea concentration (raised urea concentration defined as > 7 mmol/l)	73/101 (72%) dehydrated children and 576/1047 (55%) children without dehydration had a low bicarbonate concentration (low bicarbonate concentration defined as <21 mmol/l)	N/A
Ellis <i>et al.</i> ⁵⁷	<i>n</i> = 447 admissions (21 re-admissions) made by 426 children younger than 2 years (75% were < 1 year)	14% had moderate or severe dehydration	5 patients – no total number of patients stated 0.8% (hypernatraemia defined as serum sodium concentration of ≥150 mmol/l)	N/A	N/A	Proportion of children not stated 8% of children had raised serum urea concentration (>6 mmol/l)	Proportion of children not stated 4% of children had a low bicarbonate concentration (≤16 mmol/l)	N/A
Jenkins and Ansari ⁵⁸	<i>n</i> = 215 Age range 2 weeks to 9 years (61% were < 1 year)	15/215 (7%) with severe dehydration (>5%)	2/76 (2.6%) (hypernatraemia defined as plasma sodium concentration of >145 mmol/l) (only 35% tested)	17/76 (22%) (serum sodium concentration within the range 128–134 mmol/l) No definition of hyponatraemia given	N/A	17/76 (22%) (serum urea concentration >6 mmol/l)	13/76 (17.1%) (serum bicarbonate concentration <15 mmol/l) (lowest value 9 mmol/l)	N/A
Yurdakok and Oran ⁷⁹	<i>n</i> = 119 Age range 2 months to 15 years	109/119 (91.6%) had moderate dehydration 10/119 (8.4%) had severe dehydration	9/119 (7.6%) (hypernatraemia defined as >150 mmol/l) 1/119 (0.84%) had raised sodium of 170 mmol/l	4/119 (3.4%) (hyponatraemia defined as <130 mmol/l)	5/119 (4.2%) (hypokalaemia defined as <3 mmol/l)	N/A	58/119 (48.7%) had a low serum bicarbonate concentration (<15 mmol/l) 15/119 (12.6%) had a serum bicarbonate concentration <10 mmol/l	13/119 (10.9%) (hyperglycaemia defined as >140 mg/dl)
Reid and Losek ⁸⁰	<i>n</i> = 528 Data presented for 196/207 children with acute gastroenteritis given IV rehydration and who had serum glucose concentration data available Age range 1–57 months (mean age 23 months, SD 14 months)	No statement on the number of children with dehydration 207/528 (39%) received IV rehydration	N/A	N/A	N/A	3/16 (19%) hypoglycaemic children had raised BUN 44/150 (29%) non-hypoglycaemic children had raised BUN (raised BUN level taken as >18 mg/dl)	17/18 (94%) hypoglycaemic children had low serum bicarbonate 162/176 (92%) non-hypoglycaemic children had low serum bicarbonate (low bicarbonate level defined as <18 mEq/l)	N/A

BUN = blood urea nitrogen; IV = intravenous; SD = standard deviation.

Evidence summary

There was a lack of good-quality studies relevant to these two questions.

Result from one UK study showed that the incidence of biochemical abnormalities was significantly higher in dehydrated children compared with those who were not dehydrated, while the other two UK studies did not report separately the distribution of abnormalities among dehydrated and non-dehydrated children. Although the three studies employed variable definitions of abnormality for the various biochemical measurements, the incidence of hypernatraemia was reported to be less than 1% in the two latter studies and in the first study in non-dehydrated children. High urea levels (>6 or >7 mmol/l) were found in 5–8% of children while variation was seen regarding the incidence of acidosis. A study from Turkey found a higher incidence of biochemical abnormalities, but more than half of the children in this study were undernourished. This study also reported a positive correlation between serum sodium levels and blood glucose levels in children younger than 2 years with low bicarbonate levels. The last case series from the USA found 9.4% of children admitted to an emergency department having glucose levels < 3.3 mmol/l, and the mean duration of vomiting in these children was significantly longer compared with rest of the children admitted with gastroenteritis.

Evidence from the systematic review suggests that blood levels of bicarbonate > 15 or > 17 mEq/l (or absence of acidosis) is helpful in decreasing the likelihood of dehydration, while lower levels are not helpful in increasing the chances of detecting dehydration. High urea/BUN levels, high serum uric acid and increased anion gap were also found to be unhelpful in detecting dehydration. Results from another study indicate that urine specific gravity, urine ketone levels and low urine output are not useful diagnostic tests in detecting dehydration.

GDG translation from evidence to recommendations

The GDG found that there was a lack of satisfactory evidence with regard to the incidence of clinically important biochemical disturbances in children with gastroenteritis in the UK. One large study did indicate that hypernatraemia, uraemia and acidosis were more commonly found in those with clinical dehydration. The available studies did not, however, make clear the frequency with which such abnormalities occurred in children with varying levels of dehydration. In studies of large populations of children with gastroenteritis in the UK, the incidence of hypernatraemia was 1% or less, and those populations included children with severe dehydration. Increased plasma bicarbonate levels were significantly associated with dehydration but the practical usefulness of bicarbonate estimation to detect dehydration was unclear. Studies on the potential value of other blood and urine investigations for the detection of dehydration also failed to provide evidence in support of their use.

The GDG recognised that children with shock may develop metabolic acidosis and monitoring of the venous blood acid–base status is clinically important in such cases. Studies of acid–base status usually include the pH, pCO₂, bicarbonate, base deficit and lactate. When acidosis is detected, the underlying mechanism should be considered. Diarrhoea is often associated with substantial bicarbonate loss and this is a common cause of acidosis. In hypovolaemic shock, tissue blood perfusion is impaired and this can cause lactic acidosis. In those with acidosis due to bicarbonate loss, spontaneous resolution can be anticipated as the diarrhoea resolves. Patients with hypovolaemic shock require IV fluid bolus administration (see Chapter 5). Such fluid therapy would not be indicated in those with acidosis related to bicarbonate loss. To distinguish these two types of acidosis, the GDG suggested that measurement of the anion gap: $([Na^+] + [K^+]) - ([HCO_3^-] + [Cl^-])$ could be helpful, particularly in those with symptoms or signs of shock. If the anion gap was increased, this would suggest impaired tissue perfusion as the underlying mechanism. If the anion gap was normal, bicarbonate loss was likely to be important.

The GDG considered that routine measurement of plasma glucose was unnecessary in children who would not otherwise require a blood test. However, if there was reason to clinically suspect hypoglycaemia, for example in an infant with unexplained drowsiness, then it should be measured.

Recommendations on laboratory investigations for assessing dehydration

Do not routinely perform blood biochemical testing.

Measure plasma sodium, potassium, urea, creatinine and glucose concentrations if:

- intravenous fluid therapy is required *or*
- there are symptoms and/or signs that suggest hypernatraemia.

Measure venous blood acid–base status and chloride concentration if shock is suspected or confirmed.

5 Fluid management

Introduction

Dehydration is the major complication associated with gastroenteritis. Ideally it should be prevented through appropriate fluid management. Once clinically significant dehydration is present, effective and safe strategies for rehydration are required. Additionally, following rehydration there may be a risk of recurrence of dehydration and appropriate fluid management may reduce the likelihood of that event. In this chapter, primary and secondary prevention of dehydration and the fluid management of children with established dehydration are considered.

One of the great medical advances of the 20th century was the introduction of oral rehydration therapy (ORT). ORT refers to the restitution of water and electrolyte deficits in dehydrated patients using an oral rehydration salt (ORS) solution. The term 'ORS solution' is applied to special fluid formulations containing as essential ingredients an organic solute (for example, a carbohydrate or amino acid) and sodium chloride. Such solutes are subject to active intestinal co-transport and thereby enhance salt and water absorption. Typically, ORS solution contains glucose and sodium chloride in specified concentrations. This chapter considers the use of ORT in the fluid management of children with gastroenteritis.

5.1 Primary prevention of dehydration

Clinical questions

Can oral fluid supplementation prevent dehydration? What oral fluid strategies are most effective in preventing dehydration?

A search was undertaken to identify published research on the prevention of dehydration in children with diarrhoea and/or vomiting. Although it may appear self-evident that supplemental fluids might prevent dehydration, the effectiveness of this strategy could not be assumed. Moreover, various strategies for fluid supplementation could be considered.

Evidence overview

After primary screening of 206 articles and abstracts identified from the literature search, 20 articles were retrieved. Most of these studies had in fact assessed the effectiveness of oral fluids in the treatment of gastroenteritis and dehydration rather than in the prevention of dehydration. Only one prevention study was identified. In that study, continued breastfeeding and use of ORS solution at home were evaluated as potential strategies for preventing dehydration.

In a case-control study from Bangladesh,⁸² children aged between 1 and 35 months were selected for study inclusion if they had watery diarrhoea for 6 days or less at first presentation and had been breastfeeding up to the time of onset of diarrhoea. All were assessed for dehydration and were classified as 'cases' (with moderate to severe dehydration if there was a definite decrease in skin elasticity and presence of one or more of following signs: sunken eyes, failure to urinate for 6 hours, sunken anterior fontanelle, rapid and weak pulse) or as 'controls' (with no dehydration or mild dehydration if they did not fulfil those clinical criteria). Home ORT use was defined as giving either pre-packaged ORS solution or home-made salt and sugar solution. Information on socio-economic and demographic characteristics, medical history and fluid/feeding interventions at home was collected using a field-tested structured questionnaire administered by an interviewer. Cases and controls were recruited from the same reporting area. Observer bias was reduced by blinding the interviewers to the hypothesis being tested and by blinding both mothers and interviewer to the case and control allocation. After analysing the association of each factor of interest with dehydration and identifying various confounding variables, logistic regression analysis was conducted to identify factors independently associated with dehydration. [EL = 2+]

There were 285 cases and 728 controls. After controlling for confounding factors (lack of maternal education, history of vomiting, high stool frequency, young age and infection with *Vibrio cholerae*), the risk of dehydration was five times higher in infants whose mothers stopped breastfeeding compared with infants whose mothers continued to breastfeed following the onset of diarrhoea (OR 5.23; 95% CI 1.37 to 9.99; $P = 0.016$). Similarly, the risk of dehydration was 1.5 times higher in infants who did not receive any ORT at home compared with those who received plentiful ORT (total volume ≥ 250 ml) (OR 1.57; 95% CI 1.08 to 2.29; $P = 0.019$). Infants receiving smaller amounts of ORT (≤ 250 ml) before admission had an 18% higher risk of dehydration compared with those receiving plentiful ORT, but the risk was not statistically significant (OR 1.18; 95% CI 0.84 to 1.66; $P = 0.343$).

Evidence summary

Evidence from a case-control study [EL = 2+] indicated that cessation of breastfeeding in children with gastroenteritis was associated with an increased risk of dehydration. This study also suggested that oral fluid supplementation begun at home and given in good quantity was associated with a reduced risk of dehydration.

GDG translation from evidence to recommendation

Evidence, though limited, suggests that continued breastfeeds and provision of oral fluid supplementation to children with gastroenteritis reduces the risk of dehydration. The lack of available evidence was not surprising, given the ethical difficulties with undertaking an RCT comparing the administration and withholding of oral fluid supplementation. Given that oral fluids are effective in the management of the dehydrated child, as discussed in Section 5.2, the GDG considered that it was reasonable to assume that liberal fluid supplementation is effective in the prevention of dehydration. While it was recognised that some children may prefer other oral fluids, ORS solution has advantages (Section 5.3) and so should be used if possible for children at increased risk of dehydration (Section 4.1).

Recommendation on primary prevention of dehydration

In children with gastroenteritis but without clinical dehydration:

- continue breastfeeding and other milk feeds
- encourage fluid intake
- discourage the drinking of fruit juices and carbonated drinks, especially in those at increased risk of dehydration
- offer oral rehydration salt (ORS) solution as supplemental fluid to those at increased risk of dehydration.

5.2 Treating dehydration

Clinical question

How do ORT and IVT compare in terms of safety and efficacy in the treatment of dehydration?

In order to address this question, a systematic literature search was undertaken that led to 363 articles and abstracts being identified. Of these, 27 articles were retrieved in hard copy for review. Most of the retrieved studies were RCTs and their results had been pooled in a systematic review⁸³ discussed below. In addition to the systematic review, another RCT conducted in children with severe dehydration⁸⁴ was included. The evidence was considered in three categories:

- ORT versus IVT for children with all degrees and types of dehydration
- ORT versus IVT for children with severe dehydration
- ORT versus IVT for children with hypernatraemic dehydration.

Some of the trials included in the systematic review had compared the effectiveness of ORT with IVT in children with severe dehydration and also hypernatraemic dehydration. Those trials were considered separately under the relevant categories.

5.2.1 ORT versus IVT for children with all degrees and types of dehydration

Evidence overview

A high-quality Cochrane review⁸³ compared the effectiveness of ORT with IVT for the treatment of dehydration due to acute gastroenteritis in children. Altogether 17 trials were included comparing an IVT arm with one or more ORT arms (oral or nasogastric). Nine of the trials were conducted in high-income countries (six in the USA and one each in Canada, Australia and Finland), one trial involved participants from both the USA and Panama, and the others were conducted in relatively low-income countries. Most trials included children aged between 3 months and 5 years. One included children up to 17 years of age and three included newborn babies younger than 14 days. All but two excluded children with hypovolaemic shock – in one, children presenting with shock or severe dehydration were treated with initial IVT before randomisation. Five trials excluded children with persistent vomiting, four included such cases, and the remaining 11 did not provide any information on this matter. Overall, more children were randomised to the ORT group ($n = 1015$) than to the IVT group ($n = 796$) because some trials included more than one ORT arm.

All the included trials used ORS solution containing glucose or dextrose with sodium, potassium and chloride, but the concentration of these constituents varied. In 14 trials, ORT was administered by mouth but in four of these nasogastric tube administration was employed if necessary. In two trials, ORS solution was given exclusively by nasogastric tube but in one of these the children had previously failed to tolerate oral administration. In one trial, a combination of oral and nasogastric administration was used. The primary outcome was failure to rehydrate but the definition of failure varied between the studies. Secondary outcomes included weight gain at discharge, incidence of hyponatraemia and hypernatraemia, duration of diarrhoea, total fluid intake and total sodium intake at 6 and 24 hours. Safety outcomes included paralytic ileus, phlebitis, peri-orbital oedema, abdominal distension and seizures. A meta-analysis was conducted using the random effects model. [EL = 1++]

Randomisation was adequate in all but two of the trials. Most of the trials were small and of poor quality. As double-blinding was not possible and arrangements for allocation concealment were unclear in 16 trials, it is likely that the treatment effects could have been overestimated.

Children treated with ORT had a 4% higher risk of failure to rehydrate (using any definition) compared with IVT, and this difference was statistically significant (18 trials; risk difference (RD) 4%; 95% CI 1% to 7%) but with strong evidence of statistical heterogeneity ($I^2 = 70%$; $P < 0.001$). When sensitivity analysis was performed using a homogeneous definition of 'failure' (limited to those with persistent vomiting, persistent dehydration and shock/seizures), the RD was reduced to 2% with the lower limit of the 95% CI including the null value (RD 2%; 95% CI 0% to 4%). A subgroup meta-regression analysis was also performed using failure to rehydrate as the dependent variable but no significant cause of heterogeneity was identified. Children treated with ORT had a significantly shorter stay in hospital compared with those treated with IVT (six trials; WMD -1.2 days; 95% CI -2.38 to -0.02 days) but again there was evidence of significant heterogeneity. There were no statistically significant differences between the two groups for the other outcomes – weight gain at discharge, mean duration of diarrhoea, incidence of hyponatraemia or hypernatraemia, or the total fluid intake at 6 hours and 24 hours.

Regarding complications, the risk of phlebitis was significantly higher in the IVT group by 2% (five trials; RD $-2%$; 95% CI $-4%$ to $-1%$). More children in the ORT group developed paralytic ileus although the difference was not statistically significant. There were no differences between the two groups for the other complications and adverse effects – peri-orbital oedema, seizures or abdominal distension.

A cumulative metagraph was developed (studies by ascending year) showing that the overall estimate of failure was unlikely to change substantially with further trials. Additionally, the study sample size ($n = 1811$) provided adequate power to support the observed results regarding failure to rehydrate. However, the study lacked power to detect serious but rare adverse events in either treatment group.

Evidence summary

A well-conducted systematic review [EL = 1++] did not find any significant difference in the incidences of hyponatraemia, hypernatraemia, the mean duration of diarrhoea, weight gain or total fluid intake in children treated with ORT compared with IVT. Although ORT was associated with a 4% higher risk of rehydration failure, when the analysis was conducted using a homogeneous definition of rehydration failure, no statistically significant difference was seen. Dehydrated children treated with ORT had a significantly shorter stay in hospital and those receiving IVT had a higher risk of phlebitis but no statistically significant differences were found between the ORT and IVT groups for the other complications – hypernatraemia, paralytic ileus, abdominal distension, peri-orbital oedema or seizures. Methodologically, there was great variation between the trials with regard to the study population characteristics, composition of ORS solution and the modes of administration of ORS solution.

Cost-effectiveness evidence

The GDG identified two treatment alternatives for children with clinical dehydration as a priority for economic analysis. The results are summarised below; further details are available in Appendix A.

A decision-analytical model was developed which aimed to compare the cost-effectiveness of ORT versus IVT. All children are ultimately rehydrated regardless of which treatment they have and therefore the model assumed equal clinical effectiveness for both treatment methods. The model probabilities were based on a Cochrane review⁸³ where the primary outcome was failure to rehydrate. For patients on ORT, failure to rehydrate implies a requirement for IVT. Theoretically, IVT should be able to replace fluid lost and manage continuing losses and therefore, for the purposes of this model, it was assumed that IVT treatment ‘failure’ is where IVT is required for a longer period of time. Complications from treatment were included in the model but limited to outcomes where a statistically significant difference was reported at the 5% level in the Cochrane review. Costs were taken from standard NHS/UK sources and focused on resource use that differed between the treatment alternatives.

A cost-minimisation approach was adopted for the base case analysis, as the cheapest option is also the most cost-effective where effectiveness between alternatives is judged to be equivalent. The base case analysis showed ORT to be the cheapest option. A ‘worst case’ analysis for ORT relative to IVT was also undertaken. The rationale was to subject this cost-minimisation finding to the most vigorous scrutiny by biasing model assumptions (within plausible limits) in favour of IVT. Results of this ‘worst case’ analysis continued to favour the use of ORT as the most cost-effective method of treating children with some dehydration. Further sensitivity analysis demonstrated that the finding that ORT is cost-effective is not particularly sensitive to the baseline inputs of the model. A threshold analysis was undertaken to assess the quality-adjusted life year (QALY) gain that would be needed for IVT cost-effectiveness, given the differences in cost between the alternatives. This showed that a larger QALY gain than could ever be expected from a small improvement in time to cure (rehydrate) would be needed for the expensive treatment option (IVT) to be considered cost-effective.

5.2.2 ORT versus IVT for children with severe dehydration

Evidence overview

Two randomised trials evaluated the effectiveness and safety of ORT versus IVT in severely dehydrated children. Both of the trials were conducted in hospital settings – one in Iran and the other in Indonesia. Owing to the nature of the treatment and control protocols, blinding and allocation concealment was not done. One of these trials⁸⁴ was included in the Cochrane review described above.⁸³

In the RCT from Iran,⁸⁵ the study population included 470 children (age range 1–18 months) presenting with watery diarrhoea (>10 ml/kg per hour), vomiting (more than six times per 24 hours) and two or more signs of severe dehydration (WHO criteria). They were recruited irrespective of previous treatment and of their nutritional state, and included those presenting with shock. Inclusion and exclusion criteria were not well defined and the method of randomisation was not

clear. After admission in the hospital and recruitment in the study, the children were randomised to the oral treatment group or the IV treatment group. The oral treatment protocol consisted of two phases. In the initial rehydration phase, an electrolyte solution with osmolarity 270 mOsm/l (sodium 80 mmol/l, potassium 20 mmol/l, bicarbonate 35 mmol/l, chloride 65 mmol/l, glucose 70 mmol/l) was administered by nasogastric tube at a rate of 40 ml/kg per hour (maximum 400 ml/kg) until clinical signs of dehydration had disappeared. This was followed by a maintenance phase where another electrolyte solution with the same osmolarity but different electrolyte composition (sodium 40 mmol/l, potassium 30 mmol/l, bicarbonate 25 mmol/l, chloride 45 mmol/l, glucose 130 mmol/l) was given by bottle or nasogastric tube at a rate of 250 ml/kg per day. Children in the IVT arm were treated for shock with Ringer's lactate solution at a rate of 20–30 ml/kg as rapidly as possible or within 1 hour in those with less severe illness. A second infusion of 20–30 ml/kg was given if the clinical signs of shock persisted. Thereafter two-thirds of the fluid deficit was replaced during the first 24 hours of treatment and the remaining one-third during the second day. Abnormal fluid losses due to severe diarrhoea were replaced in both the groups but the methods were not clearly defined. Failure to rehydrate was defined as 'no change in the clinical status or worsening of the signs of dehydration within first 2 hours of treatment'. In such cases, ORT was discontinued and IVT commenced. [EL = 1–]

The baseline characteristics of the ORT group ($n = 236$) were similar to those of the controls treated with IVT ($n = 234$). In the ORT group, one child failed to rehydrate while there were no rehydration failures in the IVT group, and there was statistically no statistically significant difference in the risk of rehydration failure between the two groups (RR 2.97; 95% CI 0.12 to 72.65). The mean duration of diarrhoea was significantly shorter in the group receiving ORT than in the group treated with IVT (4.8 versus 5.5 days; MD -0.70 days; 95% CI -1.16 to -0.24 days) and children in the ORT group had a higher percentage weight gain at discharge compared with the IVT group. At 24 hours after admission, electrolyte abnormalities were recorded in 14/236 children in the ORT arm and in 29/234 children in the IVT arm. A larger number of children in the IVT group were hypernatraemic or hyponatraemic compared with the ORT group (12 versus one and 13 versus seven, respectively). Hyperkalaemia occurred in three children in the IVT group and in five in ORT group. However, none of the observed differences in electrolyte abnormalities between the two groups were statistically significant.

Vomiting (1–3 episodes during the first 6 hours) was more frequent with IVT than ORT during the rehydration phase (30% versus 19%; $P < 0.001$). There were no differences between the groups in the frequencies of abdominal distension or peri-orbital oedema. There were seven deaths in all – two in the ORT group and five in the IVT group. All who died had completed rehydration, and most had normal electrolyte levels. Four who died had a body weight below the 3rd percentile. Home follow-up was carried out for 172 of the ORT group and 169 of the IVT group, but the study did not specify the number of re-admitted patients treated with ORT and IVT.

The RCT from Indonesia⁸⁴ included 75 children (age range 1 to 59 months) with acute diarrhoea and severe dehydration. Criteria for inclusion were the presence of a palpable and countable pulse, and absence of abdominal distension and other complications. The authors did not define their criteria for severe dehydration. Following recruitment, children were randomised to the ORT or IVT group using predetermined random numbers. The ORT group received WHO-recommended ORS solution by nasogastric infusion while the IVT group received Ringer's lactate solution. In both the groups, fluid administration rates were in accordance with WHO recommendations (40 ml/kg in the first hour, 30 ml/kg in the second, 20 ml/kg in the third and 20 ml/kg in the fourth hour). However, the definition of 'rehydration failure' was not consistent for the two groups – in the ORT group it was taken as cessation of oral therapy and start of IVT due to increased frequency of vomiting and diarrhoea within the first 4 hours of treatment, while in the IVT group it was continuation of IV fluid longer than 4 hours due to excessive vomiting or seizures. [EL = 1–]

At baseline there were no statistically significant differences between the nasogastric ORT group ($n = 36$) and the IVT group ($n = 39$) in relation to mean body weight, mean frequency or duration of diarrhoea, or mean frequency or duration of vomiting before admission. In the ORT group, 3/36 children (8.3%) failed to rehydrate and in the IVT group 2/39 children (5.1%) failed to rehydrate, and this difference was not statistically significant (RR 1.63; 95% CI 0.29 to 9.17). Two children given ORT and four given IVT experienced a recurrence of dehydration after initial

rehydration but again the difference was not statistically significant. No statistically significant differences were seen for other outcomes studied – mean duration of diarrhoea, mean duration of vomiting or mean volume of fluid therapy administered. No complications were reported in either group.

Evidence summary

Neither of two RCTs [EL = 1–] comparing ORT with IVT in children with severe dehydration found a statistically significant difference in the risk of failure to rehydrate. In one of these trials, children receiving ORT had reduced duration of diarrhoea and reduced risk of vomiting during rehydration compared with those given IVT. There were no differences in the incidences of hypernatraemia, hyponatraemia or hyperkalaemia, or in the risk of complications such as peri-orbital oedema and abdominal distension. The other was a relatively small trial, and it found no statistically significant differences between the two groups for mean duration of diarrhoea or vomiting or the volume of fluid administered.

5.2.3 ORT versus IVT for children with hypernatraemic dehydration

Evidence overview

Only one study was identified that was relevant to this question. This RCT was carried out in Iran and is described above under the evidence overview of ORT versus IVT in severe dehydration.⁸⁵ In this trial, of the 470 children randomised to ORT or IVT group, 34 who received ORT and 24 given IVT were hypernatraemic at the time of admission (serum sodium > 150 mmol/l). Overall, only one child on ORT failed rehydration but the paper did not state whether this child was among those with hypernatraemia. There were no rehydration failures in the IVT group. Two of the 34 children with hypernatraemia in the ORT group and six of the 24 with hypernatraemia in the IVT group had seizures but the evidence for statistical difference was not strong (6% versus 25%; $P = 0.05$). All who experienced seizures recovered without apparent sequelae. No other outcomes were reported in relation to the children with hypernatraemia.

Evidence summary

There is a lack of high-quality evidence to compare the effectiveness and safety of ORT versus IVT in hypernatraemic dehydration. One poorly conducted RCT [EL = 1–] reported that a larger proportion of children treated with IVT experienced seizures compared with those given ORT. However, the number of subjects was small and the difference was of borderline significance. Moreover, this study did not report any other outcomes.

GDG translation from evidence to recommendation

Both ORT and IVT were shown to be effective in the treatment of dehydration. Although, overall, IVT was shown to have a marginally higher success rate in terms of reduced risk of rehydration failure, the difference was not statistically significant when a subgroup analysis was conducted employing a uniform definition of rehydration failure. Moreover, IVT is associated with various disadvantages such as the pain and distress associated with placement of an IV cannula and the risk of complications such as phlebitis or cellulitis. In addition, the cost-effectiveness analysis confirms significant benefits of ORT compared with IVT.

There was no difference in the effectiveness of IVT compared with ORT in children with severe dehydration. As discussed in Chapter 3, a range of clinical symptoms and signs may be seen in children with dehydration and these symptoms and signs may vary in degree. Although clinicians have often attempted to make a global assessment of the degree of dehydration, accurate determination of severity is probably unreliable. However, clinicians can recognise the manifestations of shock and this requires a specific fluid management strategy as discussed later in this chapter. For those children who are dehydrated to some degree but are not shocked, treatment should normally be based on ORT. Some children may exhibit clinical features (red flag symptoms and signs – see Table 4.6) that should cause special concern, suggesting that they may be at risk of progression to shock. In such cases, close and continued observation is required and if, despite ORT, there is evidence of deterioration, IVT should be commenced. Once the

circulation has been adequately restored and the child is clinically stable, management can revert to ORT if tolerated.

Although it has often been suggested that ORT is safer than IVT for children with hypernatraemic dehydration, no evidence was identified to support this view. Neither was any evidence found to suggest that there is a risk of adverse outcomes with ORT in these cases. For that reason, the GDG concluded that ORT is to be preferred in hypernatraemic dehydration.

Recommendation on treating dehydration

Use ORS solution to rehydrate children, including those with hypernatraemia, unless intravenous fluid therapy is indicated.

5.3 Optimal composition and administration of oral fluids

While the properties of ORS solution promote its effective absorption, other fluids might also have a role in the management of children with gastroenteritis. Fluids other than ORS solution are often given to children with diarrhoea and the GDG considered this practice. This section also examines the evidence regarding ORS solution composition. There has been much debate regarding the optimal constituents and their concentrations in ORS solutions. Finally, the GDG considered strategies for the administration of oral fluids to children with dehydration.

Primary screening of 403 articles and abstracts identified from the systematic literature search resulted in the retrieval of 139 articles. After reviewing hard copies of these studies, three studies were finally included under this section. Two reviews had compared high-osmolality/high-sodium ORS solution with low-osmolality/low-sodium ORS solution, while the third review compared glucose-based ORS solution with rice-based ORS solution. No study was identified to provide evidence on the effectiveness of different types of oral fluids (other than ORS solution), different regimens of ORS solution for treating dehydration, or the frequency and volume of oral fluids to be administered.

Clinical question

Which oral fluids are most effective in treating dehydration?

In a survey of American paediatricians⁸⁶ in public and private practice and of staff from a children's hospital in Boston, up to 90% reported that they would recommend the use of clear fluids other than ORS solution for children with diarrhoea. Anecdotally, such practice is common in the UK. Although ORS solution has been extensively studied and has been shown to be a highly effective fluid for the treatment of dehydration, other fluids such as tap water or fruit juices might also be effective.

Evidence overview

No published study was identified that examined the effectiveness of fluids other than ORS solution in the treatment of dehydration. However, one study⁸⁷ characterised the composition of a wide range of readily available fluids and commercially produced drinks. The analysis included tap water and about 90 commercial 'clear' fluids including soups, juices, fruit-flavoured drinks and carbonated drinks. Sodium concentrations ranged from 0.1 to 251 mmol/l, potassium concentration from 0.0 to 65 mmol/l, and osmolalities ranged from 246 to 2000 mOsm/l. Among the fruit juices tested (apple, grape, lemon, orange), none had a sodium concentration greater than 10 mmol/l or a potassium concentration less than 24 mmol/l. The osmolality of the soups tested ranged from 293 to 543 mOsm/l. Soups prepared from crystals had slightly higher osmolalities than those prepared from liquid concentrates.

Evidence summary

No study was found to evaluate the effectiveness of juices, tap water or other commercial clear fluids in the treatment of dehydration. Evidence from one cross-sectional study showed great variation in the concentration of sodium and potassium, and in the osmolality of readily available commercial clear fluids such as juices, soups and carbonated drinks.

GDG translation from evidence to recommendation

Although there were no clinical trials on the effectiveness of fluids other than ORS solution in the treatment of dehydration, the GDG considered that the composition of such fluids was generally inappropriate. In dehydration due to gastroenteritis, both water and electrolyte replacement is essential, and non-ORS solution fluids do not usually contain appropriate constituents. ORS solution was considered the appropriate fluid for oral rehydration.

Clinical question

What is the most effective composition of ORS solution?

ORS solution has been manufactured using a range of constituents in differing concentrations. Various organic solutes have been included such as glucose, starch and amino acids. Sodium chloride has been used in varying concentrations. Other non-essential constituents, including potassium, bicarbonate and acetate are often included. Much research has been carried out to evaluate the effectiveness and safety of these various solutions. Two key areas of research have focused on the optimal sodium/osmolar concentration in ORS solution and on the relative efficacies of glucose versus rice starch as the organic constituent in ORS solution.

The composition of the original WHO ORS solution (glucose 111, sodium 90, potassium 20, chloride 80 and bicarbonate 30, all in mmol/l) was selected to allow for use of a single solution that would effectively treat dehydration secondary to diarrhoea caused by various infectious agents and resulting in varying degrees of electrolyte loss.¹⁹ However, in developed countries, viral gastroenteritis is common and is associated with less severe salt losses, and so there was concern that the sodium content of the original WHO ORS solution might be excessive.⁸⁸ From the 1970s, efforts focused on improving the efficacy of ORS solution by altering its composition. It was found that solutions with higher concentrations of co-transporters (such as sugars) and higher osmolarity decreased rather than increased intestinal sodium and water absorption. Additionally, hypernatraemia was reported with their use. The current formulation WHO ORS solution adopted in 2002 (glucose 75, sodium 75, potassium 20, chloride 65 and citrate 10, all in mmol/l) preserves the 1 : 1 molar ratio of sodium to glucose that is critical for efficient co-transport of sodium. It has a reduced osmolar load (245 mOsm/l) compared with the original formulation (311 mOsm/l). It also has a longer pre-mixed shelf life owing to its citrate content.

The evidence searches on this question were limited to include only those studies that compared the effectiveness of high-osmolarity/low-sodium ORS solution with low-osmolarity/low-sodium ORS solution or the glucose-based ORS solution with the rice-based ORS solution. Evidence on other types of ORS solution using different carbohydrate substrates or organic substitutes such as cereals or amino acids was not reviewed in this section since these products are not available in the UK and are not currently recommended by the WHO.

Evidence overview

Three systematic reviews have been included – two^{89,90} provided evidence relating to effectiveness of low-sodium/low-osmolarity ORS solution versus high-sodium/high-osmolarity ORS solution, while the third review⁹¹ compared rice-based ORS solution with the glucose-based ORS solution.

One systematic review⁸⁹ compared the effectiveness of the previously recommended WHO ORS solution (osmolarity 311 mmol/l with 90 mmol/l of sodium) with reduced osmolarity ORS solution (osmolarity 250 mmol/l or less with reduced sodium) in the treatment of children with acute diarrhoea. Only RCTs with adequate randomisation were considered for inclusion while quasi-randomised trials were excluded. Participants included children with acute diarrhoea (with history of less than 5 days). The primary outcome of interest was the need for 'unscheduled' IV infusion during the course of treatment, while the secondary outcomes were stool output, vomiting and asymptomatic hyponatraemia (serum sodium < 130 mmol/l) during follow-up. Results from the various studies were pooled using the fixed effect model. [EL = 1++]

Fourteen RCTs were included in this review and they were conducted in Egypt (two), Bangladesh (three), Mexico (one), Columbia (one), India (three), Panama (one) and the USA (one). All the studies recruited children younger than 5 years suffering from acute non-cholera diarrhoea, with the exception of three trials that did include children with cholera. In five trials, children

with severe dehydration were included while five other trials included malnourished children. Nine trials reported allocation concealment that was adequate and six were double-blinded. Loss to follow-up was less than 10% of the randomised participants in all trials. The protocol of this review had initially defined reduced osmolarity as < 250 mOsm/l but during the course of reviewing this limit was increased to 270 mOsm/l or less since some trials had used this higher limit of definition. Osmolarity of the control group was also increased from 311 to 331 mmol/l to include two additional trials. Nevertheless, in both the trials the concentration of sodium and glucose was similar to the WHO-recommended ORS solution. Since stool output was measured in various ways using different units in the RCTs, their results were pooled and expressed as standardised mean difference.

Out of 14 trials, 11 reported the need for unscheduled IVT. Three trials reported that none of the children required an IV infusion and hence odds ratios could not be calculated. Results from the meta-analysis of the other eight trials ($n = 1996$) showed a significant reduction in the need for additional IVT for children receiving the low-osmolarity ORS solution compared with children treated with the WHO-recommended high-osmolarity ORS solution (OR 0.59; 95% CI 0.45 to 0.79). Sensitivity analysis conducted with studies where allocation concealment was clearly described as adequate suggested little difference in the result for the primary outcome. Eleven trials ($n = 1776$) measured stool output during the rehydration period and the pooled results showed a significant reduction in stool output with the low-osmolarity ORS solution (SMD -0.23 ; 95% CI -0.33 to -0.14). Hyponatraemia and vomiting during rehydration were reported in six trials each. Children treated with the reduced osmolarity ORS solution showed a lower tendency for vomiting (OR 0.71; 95% CI 0.55 to 0.92) compared with the WHO ORS solution group, but no statistically significant difference was observed for the presence of hyponatraemia (OR 1.44; 95% CI 0.93 to 2.24). There was no evidence of statistical heterogeneity for any of the results.

In the second systematic review from the USA,⁹⁰ the effectiveness of ORT was evaluated in comparison with IVT among well-nourished children with gastroenteritis in developed countries, and this was followed by a comparison between high-sodium ORS solution and low-sodium ORS solution. Trials were included if they were published in English, conducted in populations of well-nourished children during the late 1970s through to the early 1990s and included more than ten patients. A total of 13 trials were included in this review and all were conducted in the USA or Canada – six RCTs of ORT with IVT arms and seven RCTs without IVT arms (i.e. comparing oral solutions with differing sodium content). The age of the study population ranged from 3 months to 3 years but one study included children aged 1 month to 14 years. Clinical efficacy was defined as the success of ORT in rehydrating children with gastroenteritis within 12–24 hours of starting treatment, while failure was defined as the need to use IVT for rehydration. High sodium content was defined as a sodium level of 90 mmol/l, medium as 50–75 mmol/l and low as 26–45 mmol/l. Safety was measured by the relative incidence of hypernatraemia (serum sodium level > 146 mmol/l) and hyponatraemia (serum sodium level < 132 mmol/l) induced by the treatment. [EL = 1+]

Altogether, eight trials (one RCT with an IVT arm and seven trials without an IVT arm) had compared ORT solutions of differing sodium content and their results are reported in this section. The high-sodium formula had the lowest failure rate among the three groups at 1.9% (95% CI 0% to 5.4%), while the low-sodium group had a failure rate of 3.6% (95% CI 0% to 7.3%) and the medium-sodium group a failure rate of 5% (95% CI 1.9% to 8.1%). However, there were no statistically significant differences in the failure rates of the three groups treated with high-, medium- and low-sodium ORS solution. Only one trial with an IVT arm gave information on the cases of hypo- and hypernatraemia. It reported three cases of hyponatraemia that corrected to normal within 24 hours of treatment. Another trial with no IVT arm reported one case of hyponatraemia in the high-sodium group and six cases each in the medium- and low-sodium groups. Estimates of effect could not be calculated for incidences of hyponatraemia and hypernatraemia because the total numbers of individuals in each group were not available. Moreover, there were no statistically significant differences between the high- and low-sodium ORS solution for other outcomes (weight gain, volume, frequency and duration of diarrhoea, or length of hospital stay).

A Cochrane review⁹¹ compared rice-based ORS solution (50–80 g/l of rice powder) to the glucose-based WHO ORS solution (20 g/l of glucose) for the treatment of diarrhoea. Trials were included only if the rice-based ORS solution was made by replacing glucose in the standard WHO ORS

solution with 50–80 g/l of rice powder and all the other electrolyte concentrations remained the same. Participants included both children and adults with signs of dehydration due to acute diarrhoea. The outcomes reported were stool output during the first 24 hours, total stool output (from admission to cessation of diarrhoea) and duration of diarrhoea. For studies in children, data from girls were excluded owing to difficulty in measuring the stool volumes.

Of 22 hospital-based RCTs included for this review, 12 trials included children – five with cholera and seven with non-cholera diarrhoea. Four of these trials were conducted in Bangladesh, two in India, and one each in Indonesia, Pakistan, Mexico, Chile, Peru and Egypt. Two trials included children younger than 6 months whereas the others included children above 4–6 months. Allocation concealment was adequate in 15 of the 22 studies while the method of randomisation and concealment was not reported in the remaining studies. None of the trials reported whether patients with severe dehydration were randomised or whether outcome measurement started before or after initial IVT. In six trials, 1–15% of randomised patients were excluded from the final analysis, but these patients should have continued to be monitored and their data included using intention-to-treat analysis. Outcomes were analysed separately for children with cholera and non-cholera diarrhoea. [EL = 1++]

Twelve studies ($n = 2854$) reported the duration of diarrhoea for children younger than 5 years suffering from non-cholera diarrhoea. Results from the meta-analysis suggest that children receiving rice-based ORS solution had shorter duration of diarrhoea compared with those receiving the glucose-based ORS solution, but the difference was not statistically significant (WMD -1.26 days; 95% CI -4.4 to 1.9 days). There were also no statistically significant differences between the two types of ORS solution for the outcomes of stool output in the first 24 hours of the intervention (15 trials; WMD -4.3 g/kg; 95% CI -9.4 to 0.8 g/kg) or total stool output (nine trials; WMD -28.2 g/kg; 95% CI -52.4 to 3.9 g/kg). For children with cholera, a significant reduction in the 24 hour stool output was seen with rice-based ORS solution (four trials; WMD -67.4 g/kg; 95% CI -94.3 to -40.5 g/kg). Only one trial ($n = 48$) reported total stool output and duration of diarrhoea in children with cholera and that showed a significant decrease in both outcomes with the use of rice-based ORS solution.

Evidence summary

There is evidence from one high-quality systematic review [EL = 1++] indicating a significant reduction in the need for unscheduled IV fluids for the treatment of dehydration in children with diarrhoea when using low-osmolarity ORS solution compared with the previously recommended high-osmolarity WHO ORS solution. Moreover, the results suggest that low-osmolarity ORS solution leads to a greater reduction in stool output and vomiting. No difference was seen in the incidence of hyponatraemia. The other systematic review [EL = 1+] reported no statistically significant difference between ORS solutions with different sodium contents in terms of treatment failure (need for IVT) in well-nourished children with gastroenteritis and dehydration. It also failed to show any consistent trend in favour of either high- or low-sodium ORS solution for rehydration.

Evidence from a well-conducted systematic review [EL = 1++] found no statistically significant differences in stool output or duration of diarrhoea when children with non-cholera diarrhoea were treated with rice-based ORS solution compared with the traditional glucose-based ORS solution. However, in children with cholera, rice-based ORS solution was associated with a reduction in stool output and duration of diarrhoea.

GDG translation from evidence to recommendation

ORS solution of reduced osmolarity (<270 mOsm/l) is preferable to solutions with a high osmolarity (>311 mOsm/l). Reduced osmolarity ORS solution was associated with a lower incidence of failure to rehydrate and also a greater reduction in stool output.

The original (pre-2002) WHO ORS solution had an intermediate osmolarity of 311 mOsm/l and a sodium concentration of 90 mmol/l. In 2002, the WHO recommended a new ORS solution formulation of lower osmolarity and sodium concentration (245 mOsm/l and 75 mmol/l, respectively). This is closer in composition to the ORS solution products commonly used in the UK (sodium concentrations 50–60 mmol/l, osmolarities 240–250 mOsm/l; see Table 5.1).

Table 5.1 Compositions of WHO ORS solution and of ORS solution products available in the UK

Product	Osmolarity (mOsm/l)	Glucose (mmol/l)	Sodium (mmol/l)	Chloride (mmol/l)	Potassium (mmol/l)	Citrate (mmol/l)	Bicarbonate (mmol/l)
WHO ORS solution pre-2002	311	111	90	80	20	–	30
WHO ORS solution post-2002	245	75	75	65	20	10	–
Dioralyte® (Sanofi-Aventis)	240	90	60	60	20	10	–
Electrolade® (Thornton & Ross)	251	111	50	40	20	–	30
Rapolyte® (KoGEN)		110	60	50	20	10	–

There are no studies that compare the new (2002) WHO ORS solution with products currently used in the UK. It is therefore unknown whether there are any clinically important differences between these solutions, particularly in terms of rehydration failure, cessation of vomiting, duration or volume of stool losses, or incidence of symptomatic hyponatraemia. Hyponatraemia was important to consider as it has been suggested that low-sodium ORS solution might be associated with hyponatraemia. While some studies suggested this might be so, the effect was not statistically significant and there were no reports of clinically significant hyponatraemia with adverse effects such as convulsions. There were no studies with hyponatraemia as a primary outcome. The GDG therefore concluded that ORS solution products currently available in the UK were appropriate for use in ORT.

Cereal-based ORS solution may have a beneficial effect in reducing diarrhoeal losses compared with glucose-based ORS solution. However, the available evidence applied only to cholera and was of low quality. Rice-based ORS solution is currently not available in the UK. The GDG did not consider that there was evidence to support its use.

Clinical question

What oral fluid regimen should be used?

No studies were identified that compared the clinical effectiveness of various oral fluid regimens in the treatment of dehydrated children with gastroenteritis. Likewise, there were no studies that specifically addressed the optimal volume of fluid to be used for rehydration, the optimal route of administration (bottle, beaker, cup, spoon, syringe or nasogastric), the frequency of administration, the time interval over which rehydration should be attempted, or the indicators for reintroduction of oral fluids after IVT.

Evidence overview

Since no study was identified directly answering the question, evidence was included from three RCTs that had recruited children with dehydration for the primary purpose of comparing different ORS solution products. The study populations in all three trials included some children presenting with severe dehydration and/or shock, and all these children were started on ORT following initial rehydration with IVT.

In the first multicentre trial,⁹² the efficacy of reduced osmolarity ORS solution was compared with that of the pre-2002 WHO ORS solution. Children presenting with severe dehydration were initially rehydrated with IVT for 2 hours and then randomised to the two groups as soon as they were able to accept fluids orally. The second trial⁹³ compared oral glucose electrolyte solution with oral sucrose solution in equimolar concentrations using the WHO-recommended electrolyte formula. In children with severe dehydration (fluid deficit \geq 10% body weight), 70% of their estimated fluid deficit was replaced within the first 2 hours by IVT and further rehydration was achieved by ORT. The third trial⁹⁴ evaluated the safety and efficacy of glycine-based ORS solution compared with ORS solution containing no glycine. Children with severe dehydration in both groups were initially given IVT until blood pressure and pulse returned to normal, and then rehydration was completed within 4 hours by giving either of the two ORS solutions.

Evidence summary

There were no studies that provided direct evidence on the effectiveness of various oral fluid regimens in terms of the route of administration, frequency of administration or volume of fluid to be used. However, the procedures used in studies suggest that children with gastroenteritis and severe dehydration can be successfully rehydrated with ORT after an initial rehydration with IVT. After an initial rehydration with IVT, ORT was usually introduced within 2–4 hours of starting rehydration.

GDG translation from evidence to recommendation

There was no evidence to support recommendations on how much fluid should be given, and over what time frame, when treating a dehydrated child. The WHO recommends rehydration over a period of 4 hours.²⁰ The GDG agreed that clinical experience showed this to be generally possible. It was considered important to achieve rehydration as quickly as possible, but more rapid rehydration might be associated with an increased risk of vomiting.

The traditional approach to oral rehydration has been to offer ORS solution in small quantities at frequent intervals. That seemed appropriate advice and the GDG agreed that it would improve tolerance.

Given that precise determination of dehydration severity is not possible, the exact volume of fluid required for rehydration cannot be calculated accurately at the outset. At the mildest end of the spectrum, dehydration may be clinically undetectable. It is likely that clinical signs of dehydration first become apparent in patients with about 3–5% weight loss. Children who are at the most severe end of the spectrum may have lost 10% or more of their body weight. The GDG therefore considered that a reasonable approach in a child presenting with clinical manifestations of dehydration was to assume 5% dehydration at the outset. Based on that assumption, rehydration should be attempted by giving 50 ml/kg over the initial 4 hour rehydration period. In some cases, this may be somewhat more than is required, but that will be of no clinical consequence. In other more severely dehydrated children, 50 ml/kg may be insufficient. It would therefore be important to regularly reassess the child's state of hydration and, when necessary, to increase the final volume of replacement fluid administered (see worked example in Tables 5.2 and 5.3). Children with red flag symptoms or signs (see Table 4.6) would require frequent reassessment during rehydration, with adjustment of the deficit replacement depending on that assessment.

The use of a nasogastric tube to deliver ORS solution is common but not universal practice. It may allow oral rehydration of children who will not drink ORS solution. If children vomit ORS solution persistently, continuous infusion through a nasogastric tube may improve tolerance but there are no studies on this method of administering ORT. Placement of a nasogastric tube may be somewhat unpleasant or distressing for children. There are possible complications associated with nasogastric feeding.⁹⁶ These concerns needed to be balanced against the alternative of IVT,

Table 5.2 Worked example of an oral rehydration strategy in a 12-month-old child weighing 10 kg

Strategy	Volume	Rate
Fluid deficit for replacement over 4 hours	500 ml	125 ml/hour
Maintenance fluids over 24 hours ^a	1000 ml	40 ml/hour
Total volume for first 4 hours	660 ml	165 ml/hour
Aliquot volume if administered at 10 minute intervals		27.5 ml/10 minutes

^a Maintenance fluids⁹⁵

Table 5.3 Maintenance fluid volume requirements based on body weight

Weight (kg)	Volume per day	Volume per hour
0–10	100 ml/kg	4 ml/kg per hour
10–20	1000 ml + 50 ml/kg for each kg > 10	40 ml + 2 ml/(kg > 10)
20+	1500 ml + 20 ml/kg for each kg > 20	60 ml + 1 ml/(kg > 20)

which might also be associated with distress and complications such as phlebitis or cellulitis. The GDG considered that nasogastric fluid administration was a reasonable and perhaps preferable alternative to IVT for some children. However, each case needed to be assessed on its own merits. Moreover, studies comparing nasogastric tube therapy with IVT should be undertaken.

Recommendation on oral rehydration therapy

In children with clinical dehydration, including hypernatraemic dehydration:

- use low-osmolality ORS solution (240–250 mOsm/l)* for oral rehydration therapy
- give 50 ml/kg for fluid deficit replacement over 4 hours as well as maintenance fluid
- give the ORS solution frequently and in small amounts
- consider supplementation with their usual fluids (including milk feeds or water, but not fruit juices or carbonated drinks) if they refuse to take sufficient quantities of ORS solution and do not have red flag symptoms or signs (see Table 4.6)
- consider giving the ORS solution via a nasogastric tube if they are unable to drink it or if they vomit persistently
- monitor the response to oral rehydration therapy by regular clinical assessment.

Research recommendation

In children who do not tolerate oral rehydration therapy, is ORS solution administration via nasogastric tube cost-effective, safe and acceptable in treating dehydration compared with intravenous fluid therapy?

Why this is important

Oral rehydration therapy is normally preferable to intravenous fluid therapy for rehydration in children with gastroenteritis. However, some children may not tolerate oral rehydration therapy, either because they are unable to drink ORS solution in adequate quantities or because they persistently vomit. In such cases, ORS solution could be administered via a nasogastric tube, rather than changing to intravenous fluid therapy. This overcomes the problem of ORS solution refusal. Continuous infusion of ORS solution via a nasogastric tube might reduce the risk of vomiting. A well-conducted randomised controlled trial is needed to assess the cost effectiveness, safety and acceptability of rehydration using nasogastric tube administration of ORS solution compared with intravenous fluid therapy.

5.4 Intravenous fluid therapy (IVT)

Introduction

Although most children with dehydration can be successfully managed using ORT, occasionally IVT may be indicated. In children with hypovolaemic shock, immediate IVT might be required. For various reasons, ORT might be unsuccessful and so IVT might be necessary. The GDG considered the indications for starting IVT, the rate at which IV rehydration should be performed, the choice of IV fluid, and the option of changing from IVT to ORT to complete the rehydration process.

A systematic literature search identified 381 publications and 26 articles were retrieved for reviewing. Secondary screening of these studies led to four studies being finally included as evidence; however, these studies were of poor quality or gave indirect evidence to inform the questions. The majority of questions included in this section yielded no evidence considered to be of sufficient quality on which to base recommendations. Thus the recommendations developed in this section are based mostly on a combination of non-RCT studies, observational data, anecdotal reports and expert consensus opinion.

* The *BNF for Children* (BNFC) 2008 edition lists the following products with this composition: Dioralyte®, Dioralyte® Relief, Electrolade® and Rapolyte®.

Clinical questions

What are the indications for starting IVT for rehydration?

Evidence overview

No studies were identified which gave evidence on the indications for starting IVT in children with dehydration

GDG translation from evidence to recommendation

In the absence of any published evidence to inform this question, the GDG based its recommendation on consensus decision. The group fully accepted established practice with regard to the initial management of patients with shock.⁹⁷ Consequently, all children with hypovolaemic shock due to dehydration require IVT. Patients with severe dehydration may be at risk of becoming shocked. As discussed in Chapter 4, the clinical features associated with severe dehydration may partially overlap those associated with shock. The GDG considered that if the clinician was uncertain as to whether the child was actually in a state of shock, the child should receive IVT.

The GDG agreed that, although ORT was recommended as the first-line treatment for dehydration, it was occasionally unsuccessful. In cases where, despite appropriate treatment with ORS solution, the child's state of hydration does not improve or where it shows signs of worsening, IVT would be required. For example, a child might fail to tolerate the necessary quantities of oral (or perhaps nasogastric tube administered) ORS solution.

The decision to use IVT should only be taken, however, following a thorough assessment of the child's condition and careful consideration as to whether ORT is truly failing. It is also important that the child's state of hydration be monitored carefully and regularly.

Recommendation on when to use intravenous fluid therapy for treating dehydration

Use intravenous fluid therapy for clinical dehydration if:

- shock is suspected or confirmed
- a child with red flag symptoms or signs (see Table 4.6) shows clinical evidence of deterioration despite oral rehydration therapy
- a child persistently vomits the ORS solution, given orally or via a nasogastric tube.

Clinical questions

What is the immediate IVT regimen for shock due to dehydration? What is the optimal fluid composition for IVT in dehydration?

A range of IVT regimens and fluids have been employed in the treatment of dehydration and shock. The fluids have included Ringer's lactate and saline in various concentrations.

Evidence overview

No study was identified which specifically addressed the question of immediate IVT regimen in children with hypovolaemic shock. For the second question, one good-quality RCT was found that compared 0.9% saline plus 2.5% dextrose (NS) with 0.45% saline plus 2.5% dextrose (N/2) for the treatment of dehydration.

In the absence of any direct evidence to answer the first question, information was collected from various studies which had described fluid regimens in the treatment of dehydration in children with severe dehydration and/or shock. The various regimens are summarised in Table 5.4.

For the optimal composition of fluid for IVT, one study was identified. It was a prospective randomised study¹⁰² conducted in Australia to determine whether the use of 0.9% saline rather than 0.45% saline reduced the risk of hyponatraemia. Children with gastroenteritis aged between 6 months and 14 years were eligible for enrolment in the study only after a decision to treat with IVT was made by their treating physician, independent of the study. IVT was administered

Table 5.4 Fluid regimens used for rehydration in children in different studies

Study	Initial IVT	Oral fluid administration
CHOICE study group ⁹²	40 ml/kg per hour for 2 hours	Began once child was able to take fluids
Alam <i>et al.</i> ⁹⁸	Within 1–2 hours according to WHO guidelines	Began after initial IV rehydration
Bhargava <i>et al.</i> ⁹⁹	Ringer's lactate 20–30 ml/kg per hour until blood pressure and pulse returned to normal	Following initial IVT, rehydration completed with oral solutions
Patra <i>et al.</i> ¹⁰⁰	Ringer's lactate for 1–2 hours for those presenting with signs of hypovolaemic shock	Began after approximately 2 hours
Sack <i>et al.</i> ⁹³	70% of estimated fluid deficit replaced in the first 2 hours	Began after 2 hours
Santosham <i>et al.</i> ⁹⁴	40 ml/kg per hour of Ringer's lactate until blood pressure and pulse returned to normal ⁹⁴	Rehydration completed within 4 hours by ORT
Maulen-Radovan <i>et al.</i> ¹⁰¹	40 ml/kg per hour of Ringer's lactate solution until blood pressure and pulse improved and patients able to tolerate fluids	Hydration continued using assigned ORS solution

for dehydration if, while being treated in the emergency department, children were vomiting or had an inadequate intake of oral fluids. None of the children were severely dehydrated. After enrolment, participants were randomly allocated to receive either 0.9% saline plus 2.5% dextrose (NS) or 0.45% saline plus 2.5% dextrose (N/2). The rate of infusion was decided by the treating physician. The options used were a 'rapid replacement protocol' (RRP) consisting of 10 ml/kg per hour for 4 hours or a slow replacement protocol in which children received their fluid deficit based on estimated percentage dehydration over a 24 hour period (in addition to their maintenance fluids). The primary outcome examined was the incidence of hyponatraemia defined as plasma sodium < 135 mmol/l. The authors presented the results separately for those with hyponatraemia and those with normal plasma sodium levels measured prior to starting IVT.

Altogether, 102 children were enrolled in the study. Of these, 36% (37/102) were hyponatraemic before starting IVT. The median duration of illness prior to presentation was longer in the hyponatraemic group than in those with normal plasma sodium, but apart from this there were no statistically significant differences in their baseline clinical characteristics or biochemical test results. In total, 51 children were randomly assigned to each treatment group. In those with initial hyponatraemia given 0.45% saline ($n = 16$), there was no change in mean plasma sodium after 4 hours, but in those with an initially normal plasma sodium ($n = 35$) there was a significant decrease in the mean sodium concentration after 4 hours (135 ± 1.8 mmol/l versus 137 ± 1.7 mmol/l; $P < 0.001$). Hyponatraemic children given 0.9% saline ($n = 21$) had a significant increase in mean sodium concentration (134 ± 2.1 mmol/l versus 132 ± 2.4 mmol/l; $P < 0.001$), but in those with an initially normal plasma sodium ($n = 30$) there was no statistically significant change. [EL = 1+]

Evidence summary

No study was identified which gave direct evidence on the immediate IVT regimen in children with severe dehydration and/or hypovolaemic shock. However, processes followed in various trials suggest that these children were initially rehydrated with Ringer's lactate solution given at a rate of 20–40 ml/kg per hour over a period of 1–2 hours or until there was improvement in blood pressure and pulse volume.

Evidence from another RCT [EL = 1+] suggested that rehydration with 0.9% saline IVT led to a significant increase in the mean plasma sodium levels in children with hyponatraemic dehydration while the use of 0.45% saline did not correct this abnormality. Moreover, the use of 0.45% saline was associated with a significant decrease in the plasma sodium concentration in those with normal plasma sodium concentrations prior to IVT while the use of 0.9% saline was not.

Clinical questions

During rehydration with IVT, how much fluid is required, and how quickly should it be given? Is there a place for 'rapid rehydration therapy'?

No study was identified that provided direct evidence on the volume of deficit or the duration over which IV rehydration should be performed. For the second part of the question, three papers were identified.

Evidence overview

All three studies considered the role of 'rapid rehydration therapy' or delivering fluid deficit replacement over a short period of time in children with severe dehydration (without shock) who were unable to tolerate oral fluids.

The first was a prospective study with historical controls conducted in Australia¹⁰³ to evaluate the effectiveness of rapid rehydration with IV fluid or with ORT (administered through nasogastric tube) in the treatment of moderately dehydrated children. Inclusion criteria were age 6 months to 16 years, duration of illness less than 48 hours, presence of vomiting and diarrhoea with mild to moderate dehydration, normal respiratory rate and level of consciousness, and a CRT of less than 2 seconds. All the participants were initially given a trial of oral fluids using Gastrolyte-R® or apple juice diluted to 25% (2.5 g carbohydrate, 1.25 mg sodium, 20 mg potassium) if the former was refused. Parents were educated by nurses on the importance of initial oral rehydration. Moderately dehydrated children who were unable to tolerate 100 ml of oral fluid over 1 hour (50 ml for children younger than 2 years) were given rapid rehydration. The options for administration were intravenously using N/2 saline + 2.5% dextrose over 2 hours at 20 ml/kg per hour or by nasogastric tube with Gastrolyte-R at the same rate. Following rapid rehydration, children were given another trial of 100 ml of oral fluid (50 ml for children younger than 2 years) over 1 hour. Children who tolerated and satisfied the discharge criteria were discharged while those not tolerating orally were admitted to the hospital to continue rehydration. The historical control group was made of children admitted 2 years earlier in the same hospital with a similar diagnosis, and their hospital records were checked for data collection. These children were given a non-standard regimen of initial oral fluid trial, failing which they were rehydrated intravenously over a period of 24 hours. There was no specific education on oral fluid therapy geared towards parents and volume of fluid intake was estimated from parents' reports. Outcomes reported were admission to hospital, discharge in 8 hours or less after presentation to the emergency department and re-presentation requiring admission within 48 hours of discharge from the emergency department. The outcomes were measured for moderately dehydrated patients as well as for mildly dehydrated patients. Patients having rehydration via the IV route or the nasogastric tube route were analysed together. [EL = 2-]

In this study, 145 patients were recruited in the intervention group (rapid rehydration therapy) and 170 in the control group (IV rehydration over 24 hours). The two groups were similar with regard to age and sex but the intervention group had recruited significantly more moderately dehydrated children. On comparing moderately dehydrated patients only between the two groups, a statistically significant reduction was observed in the hospital admission rates in the intervention group compared with the control group (55.8% versus 96.3%; $P < 0.001$). Moreover, significantly more patients in the intervention group were discharged at 8 hours or less after presentation to the emergency department (44.2% versus 3.7%; $P < 0.001$). No statistically significant difference was seen for rates of re-presentation requiring admission within 48 hours of discharge from the emergency department. For mildly dehydrated patients in the two groups, no statistically significant difference was seen for the above outcomes. In the intervention group, electrolytes were analysed for 78 children and 17 were found to be hyponatraemic on initial assessment. Two of these patients presented with serum sodium levels < 130 mmol/l (128 and 125 mmol/l). However, they did not suffer from any complications or clinical sequelae and their serum sodium levels returned to normal levels by 12 hours.

The second study was a prospective cohort study from the USA¹⁰⁴ that evaluated the efficacy of rapid IV rehydration in children with mild to moderate dehydration due to gastroenteritis in the hospital outpatient department. The criteria for inclusion were age at least 6 months, clinical diagnosis of acute gastroenteritis with exclusion of other causes, vomiting for less than 48 hours

in duration with at least five episodes in the 24 hours preceding presentation, presence of normal serum sodium levels (130–149 mEq/l) and metabolic acidosis (serum bicarbonate < 18 mEq/l) at the time of presentation. Each patient received an infusion of 20–30 ml/kg isotonic crystalloid solution over 1–2 hours, followed by a trial of oral rehydration. Children who subsequently vomited were admitted for continued IV rehydration therapy, while those tolerating oral fluids were discharged with home-care instructions. To identify variables that might identify children who would not tolerate oral fluids after outpatient rapid IV rehydration, regression analysis was conducted with data from the two groups of children – those successfully tolerating oral fluids and those requiring admission for continued IVT. [EL = 2–]

This study enrolled a convenience sample of 58 children with age ranging from 6 months to 13 years (median age 22 months). One-third of the children were clinically assessed to have moderate dehydration (deficit of 6–10 % body weight) while the rest had mild dehydration. After rapid outpatient IV rehydration, 16 patients (28%) did not tolerate oral fluids while the rest 42 (72%) tolerated orally and were discharged home. The baseline characteristics of these two groups were not described. Of the discharged patients, 14% (6/42) were re-admitted owing to recurrent vomiting and dehydration. A significantly higher proportion of children who did not tolerate orally after rapid IV rehydration had metabolic acidosis (69% versus 2%; $P < 0.001$) and were moderately dehydrated (56% versus 24%; $P < 0.01$) compared with the patients discharged home. There were no differences between the two groups regarding the age and severity of diarrhoea or vomiting.

In another non-comparative study, from Canada,¹⁰⁵ children aged between 1 and 6 years with mild or moderate dehydration secondary to gastroenteritis were recruited. Children were included if they had diarrhoea and/or vomiting for less than 5 days with mild to moderate dehydration, had normal nutritional status and were unable to retain small amounts of clear fluid or refused to take them. Children who had taken medication, those having an underlying disease and those with electrolyte abnormalities were excluded. A trial of rehydration was initially attempted with small amounts of clear fluids (the authors did not specify how they defined 'clear fluid'), and if the fluid was refused or vomited, the child was considered for the study. IVT was administered by giving 3.3% dextrose and 0.3% saline at a rate of 10 ml/kg per hour for 3 hours (total 30 ml/kg). During IVT, patients did not receive any oral fluid. Discharge was allowed if there were no clinical signs of dehydration, no persistent vomiting, normal central nervous system examination and if the parents felt the child had improved. [EL = 3]

Seventeen children (mean age 2.6 ± 1.7 years) met the study inclusion criteria. All had had vomiting for an average 2.1 ± 1.2 days prior to presentation at the emergency department, and 10 of them had had diarrhoea for the preceding 1.9 ± 1.9 days. Seven children had at least 6% dehydration and 7/12 (58.3%) had mild metabolic acidosis with a base deficit of 5 or more. All patients improved after IVT and only 6/17 had vomited after therapy. One patient continued vomiting till 48 hours after IVT and required another course of IVT, following which there was no vomiting. None of the patients required hospital admission after discharge from the emergency department.

Evidence summary

There was a lack of good-quality evidence available for the clinical effectiveness of rapid IV rehydration in children with gastroenteritis and moderate or severe dehydration. The first study with a historical control group [EL = 2–] suggested that rapid rehydration by ORT or IVT in moderately dehydrated children led to a significant reduction in the hospital admission rate and an increase in discharge from the emergency department within 8 hours of presentation. No statistically significant difference was seen for these outcomes in the group of mildly dehydrated children. Results from the other two studies (a poorly conducted cohort study and a non-comparative study) showed rapid IVT to be successful in achieving rehydration in most of the dehydrated children. However, the study population in these two studies was not homogeneous and included children with mild dehydration. In the cohort study, more than 70% of the children given rapid rehydration were able to tolerate orally and the majority of children not tolerating orally had metabolic acidosis and/or moderate dehydration.

GDG translation from evidence to recommendation

There was no definitive evidence on the optimum IV fluid regimen for the management of hypovolaemic shock in the dehydrated child with gastroenteritis. However, there was widespread consensus that whatever the cause of shock, a bolus of IV fluid should immediately be given.^{97,106}

Currently, the main focus of discussion regarding fluid administration in patients with shock is on the optimal choice of fluid. This includes discussion of crystalloid versus colloid fluids, especially in relation to septicaemic or critically ill patients. The use of albumin solutions in particular is controversial.^{107–109} The GDG considered that for children with shock due to dehydration from gastroenteritis, 0.9% sodium chloride solution is an appropriate and readily available fluid for bolus administration.

In hypovolaemic shock associated with gastroenteritis, rapid recovery would be expected in most children following the administration of a 20 ml/kg bolus of 0.9% sodium chloride solution.^{97,106} If an immediate response does not occur, a further 20 ml/kg bolus should be given. In the absence of prompt response to bolus fluid administration, it is important to consider whether factors other than hypovolaemia, for example septicaemia, might be responsible. In this case, expert advice should be sought from a paediatric intensive care specialist.

With regard to the treatment of dehydration (as opposed to shock) with IVT, the GDG recognised that there was a lack of evidence from clinical trials to inform practice in this area. For example, the WHO recommends the use of Ringer's lactate solution for IV rehydration. There has been much discussion on the optimal choice of IV maintenance fluids for children, particularly since the National Patient Safety Agency (NPSA) issued a specific alert on this matter in 2007.¹¹⁰ The NPSA alert reinforced an existing trend away from the use of hypotonic solutions such as 0.18% sodium chloride. This reflected concerns about the risk of hyponatraemia.¹¹¹

The NPSA has recommended the use of isotonic solutions such as 0.9% sodium chloride with or without 5% glucose for children with a range of conditions associated with a risk of hyponatraemia, including those with diarrhoea. There has been some controversy regarding the NPSA recommendations. The use of 0.9% sodium chloride solution provides more salt to the child than is to be found in an average diet. It appears that most children do not experience adverse effects with this increased salt load, but some may do.¹¹² Concern has been expressed at a possible risk of hypernatraemia and hyperchloraemic acidosis. However, because gastroenteritis is associated with increased salt losses, the use of 0.9% sodium chloride solution in these children has not been challenged. Furthermore, the NPSA recommendations emphasise the importance of careful monitoring of plasma electrolytes during IVT.

The GDG agreed with the NPSA recommendations on this matter. The GDG also considered that it was important for clinicians to be aware that metabolic acidosis might not be due to persisting shock. Such misinterpretation could lead to the administration of excessive fluid.¹¹³

As discussed earlier in relation to ORT, there is usually no precise way of determining the exact fluid deficit and hence the required replacement volume. If a child is considered to be in a state of hypovolaemic shock, their intravascular volume has been significantly depleted owing to fluid loss. To reach this stage, it is generally accepted that they are at least 10% dehydrated, i.e. they will have lost at least 100 ml/kg of total body fluid. The GDG agreed that once shock was corrected with fluid bolus administration, it was safest to assume that the child might be 10% dehydrated and they should therefore receive 100 ml/kg as deficit replacement.

For those who are dehydrated but without shock, in keeping with the recommendation for ORT, a volume of 50 ml/kg IV was considered by the GDG to be an appropriate initial deficit replacement volume. Regular reassessment would be necessary to determine whether this was sufficient to reverse the signs of clinical dehydration. Further replacement would be given subsequently if this was necessary.

The GDG was conscious of a lack of high-quality evidence regarding the optimal time period over which IV fluids should be administered to children with dehydration. With ORT it is widely accepted that rehydration can and should be completed quickly – typically over a 4 hour period. Traditionally, IV rehydration has been performed over a 24 hour time period, and this approach is still in common use. This practice probably evolved from experience with the use of subcutaneous fluid replacement in children in the 1940s.¹¹⁴ The NPSA patient safety alert on IV infusions for

children¹¹⁰ stated that fluid deficits should be replaced over a minimum of 24 hours. That alert was published with the intention of minimising the risk of hyponatraemia when administering IV infusions to children. The GDG was conscious of the fact that opinions regarding the optimal rate of IV fluid replacement in dehydration due to gastroenteritis are varied, and more rapid rehydration regimens have been widely advocated. In 1996, the American Academy of Pediatrics recommended a rapid rehydration model, for example giving 20 ml/kg or more over the first hour depending on the individual child's clinical condition.⁵ For many years, the WHO has advocated rapid IV rehydration for severe dehydration, recommending administration of 100 ml/kg over the first 6 hours, and even more rapid rehydration in older children.⁷⁶ The GDG was aware of an increasing trend towards the use of rapid IV rehydration regimens in children with gastroenteritis, as illustrated by the studies listed in Table 5.4. It has been argued that rapid administration of IV fluids may improve gastrointestinal perfusion so that oral feeding can be reinstated earlier, and that improved renal perfusion may assist in correcting acidosis and electrolyte imbalances.¹¹⁴ The GDG was aware of a study on rapid IV rehydration currently in progress at The Hospital for Sick Children, Toronto, Canada (see www.clinicaltrials.gov/ct2/show/NCT00392145). In this trial, children attending the emergency department with dehydration secondary to gastroenteritis and requiring IV rehydration are being randomised to a 20 ml/kg 0.9% normal saline bolus over 1 hour or to 'rapid intravenous rehydration' consisting of a 60 ml/kg 0.9% normal saline bolus over 1 hour. The primary outcome measure in this study is the clinical rehydration status after 2 hours, and secondary outcomes include duration of hospitalisation and ability to tolerate oral rehydration.

The GDG concluded that it was not currently possible to make a clinical recommendation on the optimal rate of IV fluid administration in children with dehydration due to gastroenteritis. The GDG considered that this was a crucially important matter, and a priority area for research. A research recommendation was therefore made regarding rapid IV rehydration. Importantly, the GDG did recommend early implementation of ORT to complete rehydration as soon as fluids are tolerated.

The GDG considered that it is essential that plasma electrolyte concentrations are measured at baseline when commencing IVT, and regularly thereafter. The NPSA patient safety alert on administering IV infusions to children emphasises the importance of monitoring the plasma sodium concentration regularly in order to avoid dangerous hyponatraemia or hypernatraemia.¹¹⁰ The GDG did not consider that it could make precise recommendations on the frequency with which blood testing should be undertaken, and this would depend both on the results of prior tests and on the particular risk factors in individual cases. Moreover, it did not consider that it should provide specific advice on the actions needed in the event of electrolyte disturbances being present. Consideration should be given to including potassium supplementation in the IV fluid solution following measurement of the plasma potassium concentration. The fluid solutions recommended in this guideline are all available preconstituted with potassium, at either 10 mmol/l or 20 mmol/l.

The GDG recognised the specific risks associated with hypernatraemic dehydration in gastroenteritis and the importance of safe management. In such cases, expert advice on fluid management should be sought. No high-quality evidence was found on the relative safety of different fluid regimes. However, the GDG recognised that there is common agreement that in those with clinically significant hypernatraemia (plasma sodium concentration > 160 mmol/l), fluid deficit replacement should be delivered slowly (typically over 48 hours) using an isotonic solution (0.9% sodium chloride solution). The NPSA advice on IV infusions is that plasma sodium should be reduced at a maximum rate of 0.5 mmol/l per hour, or more slowly if it has prevailed for more than 5 days. Frequent monitoring of the plasma concentration is therefore essential in such patients.

Recommendations on intravenous rehydration therapy

Treat suspected or confirmed shock with a rapid intravenous infusion of 20 ml/kg of 0.9% sodium chloride solution.

If a child remains shocked after the first rapid intravenous infusion:

- immediately give another rapid intravenous infusion of 20 ml/kg of 0.9% sodium chloride solution *and*
- consider possible causes of shock other than dehydration.

Consider consulting a paediatric intensive care specialist if a child remains shocked after the second rapid intravenous infusion

When symptoms and/or signs of shock resolve after rapid intravenous infusions, start rehydration with intravenous fluid therapy.

If intravenous fluid therapy is required for rehydration (and the child is not hypernatraemic at presentation):

- use an isotonic solution such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose, for fluid deficit replacement and maintenance
- for those who required initial rapid intravenous fluid boluses for suspected or confirmed shock, add 100 ml/kg for fluid deficit replacement to maintenance fluid requirements, and monitor the clinical response
- for those who were not shocked at presentation, add 50 ml/kg for fluid deficit replacement to maintenance fluid requirements, and monitor the clinical response
- measure plasma sodium, potassium, urea, creatinine and glucose at the outset, monitor regularly, and alter the fluid composition or rate of administration if necessary
- consider providing intravenous potassium supplementation once the plasma potassium level is known.

If intravenous fluid therapy is required in a child presenting with hypernatraemic dehydration:

- obtain urgent expert advice on fluid management
- use an isotonic solution such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose, for fluid deficit replacement and maintenance
- replace the fluid deficit slowly – typically over 48 hours
- monitor the plasma sodium frequently, aiming to reduce it at a rate of less than 0.5 mmol/l per hour.

Research recommendation on intravenous rehydration therapy

In children who require intravenous fluid therapy for the treatment of dehydration, is rapid rehydration safe and cost-effective compared with the common practice of rehydration over 24 hours?

Why this is important

Most children with clinical dehydration should be treated with oral rehydration therapy, but some require intravenous fluid therapy because they are shocked or they cannot tolerate oral rehydration therapy. Rehydration with oral rehydration therapy is usually carried out over a period of 4 hours. Rehydration with intravenous fluid therapy has traditionally been undertaken slowly – typically over 24 hours. The National Patient Safety Agency has advised* that intravenous fluid deficit replacement should be over 24 hours or longer. Consequently, children will remain dehydrated and in hospital for a prolonged period. The WHO recommends that intravenous rehydration should be completed in 3–6 hours.† Many experts now support rapid intravenous rehydration, suggesting that it allows oral fluids to be started earlier and can shorten the duration of hospital treatment. Randomised controlled trials are needed urgently to examine the safety and cost-effectiveness of rapid intravenous rehydration regimens compared with slow intravenous rehydration.

Clinical questions

During rehydration, when should patients on IVT change to ORT?

Evidence overview

In the absence of any direct evidence to answer this question, information was again collected from various studies which had described fluid regimens in which ORS solution was introduced

* National Patient Safety Agency. Alert no. 22, Ref: NPSA/2007/22. Issued: 28 March 2007.

† World Health Organization. *The Treatment of Diarrhoea: a Manual for Physicians and Other Senior Health Workers*. Geneva: WHO; 2005 [whqlibdoc.who.int/publications/2005/9241593180.pdf].

after a period of initial IVT in children with severe dehydration and/or shock. The different fluid regimens have been tabulated in Table 5.4. In these studies, rapid IV fluid was given initially (for example, 20–40 ml/kg per hour) and ORT usually introduced after about 1–2 hours to complete the rehydration process.

Evidence summary

No direct evidence was identified on the appropriate time for switching IVT to ORT. Processes followed in various studies indicate that children with severe dehydration and/or hypovolaemic shock were initially rehydrated with IVT over a period of 1–2 hours or until there was improvement in blood pressure and pulse volume, and ORT were usually introduced after this period to complete the rehydration process.

GDG translation from evidence to recommendation

In current practice the GDG believed that once IVT is begun, children often remain in hospital for lengthy periods, for example 24 hours or more. Although formal research trials are not available, nevertheless clinical studies have reported success with regimens in which children with shock or severe dehydration due to gastroenteritis received IVT for 1–2 hours, with subsequent rehydration given as ORT. Hence there was some evidence (Table 5.4) to support early introduction of ORT in those requiring initial IV rehydration. The GDG agreed that if a child is able to tolerate orally, IVT should be stopped as soon as possible and further rehydration completed with ORT alone. This was desirable in that it would reduce the risk of prolonged IV fluid administration. The GDG also anticipated that early introduction of ORT could reduce the need for hospital admission and facilitate early hospital discharge.

Recommendation on changing to ORT during intravenous fluid therapy

Attempt early and gradual introduction of oral rehydration therapy during intravenous fluid therapy. If tolerated, stop intravenous fluids and complete rehydration with oral rehydration therapy.

5.5 Fluid management following rehydration

Introduction

Following rehydration, some children may be at risk of recurrence of dehydration. In those cases, it might be possible to prevent this by giving supplementary fluids. The GDG wished to consider the circumstances in which this should be advised and an appropriate strategy for effective supplementation.

Clinical questions

What is the risk of recurrence of dehydration? What interventions and/or supplementary fluid (if any) are safe and effective in preventing recurrence?

Evidence overview

A detailed literature search failed to identify any relevant good-quality studies to answer these questions.

GDG translation from evidence to recommendation

In the absence of clinical studies on the recurrence of dehydration, the GDG based its recommendations on consensus. Once a child is rehydrated, whether by ORT or IVT, it is important to ensure that they receive adequate fluids for normal maintenance and if necessary to compensate for significant ongoing fluid loss from diarrhoea. The frequency with which dehydration recurs following successful rehydration is not clear, but recurrence of dehydration certainly does happen. Intuitively, it seemed probable that some children would be at increased

risk of recurrence, for example very young infants, those with continuing severe diarrhoea and those with persistent vomiting in whom oral fluids might not be tolerated.

There were therefore many variables to consider. The GDG considered that each individual child should be assessed for risk and managed appropriately. No prescriptive recommendation could be made regarding the exact volume or frequency of supplementary oral fluid that might be required. However, the GDG agreed that in general the aim should be to offer the infant or child plenty of their normal fluids. Supplementary ORS solution could be used if practical and appropriate – particularly for those at increased risk of dehydration (Section 4.1). The WHO previously advised giving 10 ml/kg of ORS solution after each diarrhoeal stool and more recently giving 50–100 ml if younger than 2 years and 100–200 ml if above 2 years.²⁰ The post-rehydration diarrhoeal losses in the WHO recommendations' intended population (including children with cholera) are probably greater than is often the case in children in the UK. The GDG considered that specific fluid supplementation regimens are not necessary for most children. However, they should be considered for children at increased risk of dehydration, and a pragmatic approach is to give an additional 5 ml/kg of ORS solution for each large watery stool passed. It is important to bear in mind that if, for some reason, a child remains on IVT following rehydration they too might be at risk of dehydration recurrence, and they too might require fluid supplementation.

The GDG also agreed that if dehydration recurs, fluid management should be started again with the ORT.

Recommendations on fluid management following rehydration

After rehydration:

- encourage breastfeeding and other milk feeds
- encourage fluid intake
- in children at increased risk of dehydration recurring, consider giving 5 ml/kg of ORS solution after each large watery stool. These include:
 - children younger than 1 year, particularly those younger than 6 months
 - infants who were of low birthweight
 - children who have had more than five diarrhoeal stools in the previous 24 hours
 - children who have vomited more than twice in the previous 24 hours.

Restart oral rehydration therapy if dehydration recurs after rehydration.

6 Nutritional management

Introduction

Prior to the onset of gastroenteritis, children will be receiving nutrition from a range of sources. They may be breastfeeding, taking an infant formula or other fluids, or they may also be taking various solid foods. Recommendations regarding feeds must take into account this variation. Breastfed infants tend to feed frequently and in smaller volumes at each feed, and gastric emptying may be more rapid compared with those who are formula-fed.¹¹⁵ Breastfed infants may also be better able to self-regulate their feed volume.

Healthcare professionals and parents are usually most concerned about fluid management or the alleviation of symptoms. However, the nutritional aspects of management are also important. The aim of this chapter is to clarify the evidence surrounding nutritional management so that appropriate and consistent recommendations may be made. Cultural differences may be important here and should be taken into account when considering the advice given.

Anecdotally, there is wide variation in the advice given to parents regarding continuation or resumption of feeds, and regarding the types of fluids and solid foods that should be given. Advice offered has ranged from continued feeding to discontinuation of all nutrition for 24 hours or even longer. It has been common practice to recommend initial dilution of milk following its reintroduction. Some have recommended the use of specialised therapeutic feeds such as lactose-free milks, and soya or protein hydrolysate-based formulas. Some of this advice has been based on empirical considerations. For example, transient mucosal lactase deficiency is a common phenomenon with gastroenteritis and this has led to widespread use of use of lactose-free formulas. However, much of the advice offered regarding nutrition may not have had a secure evidence base.

6.1 Feeding during rehydration

Current recommendations commonly suggest that during the rehydration phase of therapy breastfeeding should continue but other food (for example, formula feeds or solid foods) should be discontinued until the child is rehydrated.^{17,19,116} This period of rehydration usually lasts for about 3 or 4 hours.

Clinical question

Should children with gastroenteritis continue the following types of feeding during the rehydration phase of therapy?

- a) breastfeeding
- b) cow's milk formula feeding
- c) mixed feeding (bottle/formula and breastfeeding)
- d) solid food/weaning food

Out of 30 retrieved papers, three studies were found to be suitable for inclusion and all of them had looked at breastfeeding during rehydration. For the other sub-questions related to formula feeding, mixed feeding and solid or weaning foods, the evidence was not considered suitable or relevant to answer the questions in a manner consistent with the standards required for guideline development.

Evidence overview

The first study was an RCT from Burma assessing the effects of breastfeeding during acute diarrhoea on clinical outcomes, while the other two papers were case-control studies (from India and Bangladesh) investigating the risk of dehydration associated with discontinuation of breastfeeding.

In the first RCT, conducted in Burma,¹¹⁷ 52 children admitted to hospital for acute watery diarrhoea of less than 48 hours' duration were recruited. The children were aged 6–24 months, had moderate or severe dehydration and had been normally breastfed. Excluded from the study were children with concomitant illness, bottle-fed children, and those who had received antibiotics before admission. After enrolment, the children were randomised (by random numbers) to receive either ORS solution alone ($n = 26$) or ORS solution plus breastfeeding ($n = 26$) during the first 24 hours in the hospital. In the second 24 hours, all children received breastfeeding and ORS solution. Children requiring IVT were given IV rehydration fluids until they had no clinical signs of dehydration and they were then randomly allocated to receive one of the two rehydration regimens. Sample size was calculated prior to the study but no details were given about concealment of allocation.

The baseline demographic characteristics of the two groups were similar, including the number of children requiring IV fluids and the number of children having *Vibrio cholerae* detected in stool swabs. Children receiving breastfeeding plus ORS solution had, on average, passed five fewer stools than those receiving ORS solution alone (12.1 ± 1.1 versus 17.4 ± 2.3 ; $P < 0.05$) and this difference was statistically significant. These children also required significantly less amount of ORS solution (ml per patient) during the early phase of diarrhoea (1570 ± 113 ml versus 2119 ± 192 ml; $P < 0.05$). However, there were no statistically significant differences between the two groups regarding duration of diarrhoea in hospital, stool output (ml/kg) or vomitus output (ml per episode). [EL = 1+]

A case–control study conducted in India⁶⁹ recruited 379 infants with acute gastroenteritis of less than 24 hours' duration. This study is described in detail in Section 4.1. Cases were defined as infants with moderate or severe dehydration ($n = 243$), while controls had no or mild dehydration ($n = 136$). More than one-quarter of cases and 21% of control children had cholera. Univariate analysis identified various factors associated with increased risk of dehydration but, after controlling for confounding variables, only two factors were found to be significantly associated: withdrawal of breastfeeding during diarrhoea (OR 6.8; 95% CI 3.8 to 12.2; $P < 0.001$) and not giving ORS solution during diarrhoea (OR 2.1; 95% CI 1.2 to 3.6; $P = 0.006$). [EL = 2+]

Another case–control study conducted in Bangladesh⁸² considered withdrawal of breastfeeding during acute diarrhoea as a risk factor for dehydration. Children were selected for study if their age was between 1 and 35 months, if they had watery diarrhoea for 6 days or less at first presentation and if they had been breastfeeding up to the time of onset of diarrhoea. The cases comprised 285 moderately and severely dehydrated children and 728 children with no clinical signs of dehydration were recruited as controls. Detailed information about the population characteristics and the study methodology is provided in Section 5.1. After controlling for confounding factors (lack of maternal education, history of vomiting, high stool frequency, young age and infection with *Vibrio cholerae*), the risk of dehydration was five times higher in infants whose mothers stopped breastfeeding compared with infants whose mothers continued to breastfeed following the onset of diarrhoea (OR 5.23; 95% CI 1.37 to 9.99; $P = 0.016$). [EL = 2+]

Evidence summary

Results from one RCT with EL = 1+ show that there was a significant reduction in the number of stools passed in the hospital in children receiving breastfeeding along with ORS solution compared with children receiving only ORS solution. However, no statistically significant differences were found between the two groups for the duration of diarrhoea or the amount of stool and vomitus. Two case–control studies did not address the question directly but their results indicated that continuation of breastfeeding during gastroenteritis was associated with a reduced risk of becoming dehydrated. No study was identified which looked at the effectiveness of continuing feeding with the other types of foods during rehydration.

GDG translation from evidence to recommendation

The GDG was aware of advice in other guidelines that encourages continuation of breastfeeds during rehydration but cessation of other milk and solid feeds. The GDG recognised that there was some evidence suggesting that breastfeeding actually confers benefit in terms of a reduction in the number of diarrhoeal stools, but no such evidence was available for other milk feeds

and solid feeds. The GDG considered that cessation of breastfeeding even for a few hours could pose significant difficulties for mother and child (for example, discomfort and possible risk to maintaining breastfeeding). For these reasons, breastfeeding should continue if possible throughout the period of rehydration.

With regard to milk formula feeds and solid foods, different considerations apply. Such feeds could result in a reduced rate of gastric emptying. Delayed emptying might increase the risk of vomiting and consequently of ORT failure. The GDG considered that the nutritional significance of any milk or solid food taken in the 3–4 hour rehydration phase of therapy is likely to be small. The GDG therefore agreed that feeds other than breast milk should be discontinued during the rehydration phase of fluid therapy. An exception to this could be made in children without red flag symptoms or signs of dehydration (see Table 4.6). If such children do not take an adequate amount of ORS solution they could be given supplementary feeds with their usual fluids – generally milk or water. However, they should not be given any fruit juices or carbonated drinks as these are often of high osmolarity and can worsen diarrhoea.

Recommendation on feeding during rehydration

During rehydration therapy:

- continue breastfeeding
- do not give solid foods
- in children with red flag symptoms or signs (see Table 4.6), do not give oral fluids other than ORS solution
- in children without red flag symptoms or signs (see Table 4.6), do not routinely give oral fluids other than ORS solution; however, consider supplementation with the child's usual fluids (including milk feeds or water, but not fruit juices or carbonated drinks) if they consistently refuse ORS solution.

6.2 Feeding following rehydration

The timing of the re-introduction of nutrition, whether as milk feeds or solid foods, may be important. Prolonged withholding of food may result in malnutrition. It is also clear that the presence of nutrients in the gut promotes mucosal health and absorptive function. It is important to appreciate that diarrhoea often persists for days but this does not usually indicate clinically significant malabsorption. A more important indicator of recovery is the achievement of appropriate weight gain.

The common practice of diluting feeds during the process of re-introduction could have adverse consequences for recovery. It has also been suggested that the use of specialised soy protein or protein hydrolysate formulas may reduce the risk of complications during recovery from gastroenteritis. Lactose-free or lactose-reduced formulas have been recommended to reduce the risk of diarrhoea from lactose malabsorption.

Solid foods may be important during the recovery phase, not only in the prevention of malnutrition but also in promoting mucosal recovery. There have been suggestions that specific foodstuffs could also promote recovery. In some cultures, the use of specific foods such as rice and cereal-based foods has been promoted. The evidence available regarding such practices was identified in order to inform recommendations.

Clinical questions

- Does early versus late re-introduction of feed affect outcomes?
- What milk or other liquid feeds should be allowed?
- Should solid foods be allowed? If yes, what foods should be allowed?
- What are the indications for use of a specialised formula?

Out of 71 retrieved papers, 28 were found to be suitable for inclusion and addressed maintenance feeding following the rehydration phase of therapy. Five RCTs compared the effect of early versus late reintroduction of feed on clinical outcome while six RCTs described graded re-feeding versus full-strength re-feeding regimens. One RCT described the addition of fruit juices to the

post-hydration diet. A further seven RCTs investigated which solid foods may be suitable for the re-feeding period. For the last sub-question, there were three RCTs comparing lactose with lactose-free cow's milk feeds and three comparing soy formula with lactose-containing formula. One RCT compared the effectiveness of soy formula in early and late re-feeding and two others compared cow's milk formula versus a special formula.

6.2.1 Early versus late re-introduction of feed

Evidence overview

Five studies (three RCTs and two quasi-randomised trials) compared the effectiveness of early feeding with late feeding.

A multicentre RCT involving 12 European hospitals¹¹⁸ was conducted to compare the effect of early or late feeding on the duration and severity of diarrhoea, weight gain and complications in weaned infants ($n = 230$) younger than 3 years who were hospitalised with acute diarrhoea (duration more than 1 but less than 5 days). Excluded were children with short gut syndrome, chronic inflammatory bowel disease, ileus, previous treatment with antidiarrhoeal drugs, associated hepatic or renal disease, and those already receiving ORS solution or on IV fluids. After appropriate rehydration with ORS solution over a period of 4 hours, the children were allocated by random numbers to receive either their usual diet (early feeding group $n = 134$) or continue ORS solution only for 20 hours followed by their usual diet (late feeding group $n = 96$). In addition, both groups were offered ORS solution (10 ml/kg) for each watery stool. Breastfed children received ORS solution and diet in addition to breastfeeding. On comparing the baseline characteristics of the two groups, it was found that there were statistically significant differences between the two groups regarding the age of introduction of solid foods, proportion of children presenting with blood in stools, proportion of children with rotavirus detected and incidence of lactose intolerance, but it was not clear whether these factors had been adjusted during the final data analysis. Moreover, limited data were given for the results and they were expressed mainly in graphs. The authors found mean weight gain in the early feeding group to be significantly greater compared with the late feeding group at both 24 hours ($P = 0.01$) and during hospitalisation ($P = 0.001$), but the weight gain at day 5 and day 14 was similar in both the groups. There were also no statistically significant differences between the two groups for the duration of diarrhoea or the incidence of watery stools or vomiting on days 1–5. [EL = 1–]

In a four-armed RCT carried out in Peru,¹¹⁹ 138 hospitalised male children aged between 3 and 36 months with diarrhoea and dehydration (mild to severe) were recruited. Excluded from the study were children receiving more than one breastfeeding per day, those who received more than a single dose of antibiotics, those who had had an episode of diarrhoea within the previous 3 weeks, and those with poor nutritional status (weight-for-length < 2 SD below the national standard). Children ($n = 10$) were also excluded from the data analysis if they did not remain in the hospital for the study period. After initial rehydration for 2–4 hours with ORS solution according to WHO guidelines (except Group 4 which received IVF for rehydration), children were assigned to four dietary groups by a block randomisation procedure. These groups were:

- Group 1 ($n = 31$): full-strength formula based on casein, sucrose, dextrin, maltose, soybean oil and cotton oil with a vitamin–mineral mix added
- Group 2 ($n = 29$): half-strength formula with the same composition as Group 1 for the first 48 hours, followed by full-strength formula
- Group 3 ($n = 34$): ORS solution continued for the first 48 hours followed by half-strength formula for the next 48 hours and then full-strength formula
- Group 4 ($n = 34$): IV fluids (no oral fluids) for the first 48 hours followed by half-strength formula for the next 48 hours and then full-strength formula.

Thus by day 5, children in all four groups received the same dietary therapy. The main outcome measures were changes in body weight and duration of diarrhoea over a 2 week period. The baseline characteristics of the four groups were similar but data on the outcomes were either presented graphically or were not presented clearly. It was seen that, although all groups gained weight during the first 12 hours in the hospital, only children in Group 1 were able to maintain a positive weight trend after 24 hours. When the combined Groups 1 and 2 were compared with combined Groups 3 and 4 at 2 weeks after admission, the difference in weight increments was

stated to be statistically significant ($t = 2.14$; $P < 0.004$). The children in the former two groups gained on average 140 g more than those in the latter groups. However, the authors did not report statistically significant differences in the duration of diarrhoea or therapeutic failure rates (defined as recurring dehydration, worsening electrolyte abnormalities or prolonged severe diarrhoea) between the four groups. [EL = 1–]

Another RCT, from Pakistan,¹²⁰ recruited 69 boys aged between 9 and 48 months with acute watery diarrhoea (duration less than 3 days), moderate or severe dehydration, no previous antibiotic treatment and no complication other than those directly related to dehydration, and who were weaned from mother's milk. Criteria for exclusion were severe systemic illness, severe malnutrition, oedema or fever more than 101 °F. After initial rehydration with ORS solution or IVT (duration not given), children were randomly allocated (using a random number table) to the two groups:

- Group A (late feeding group $n = 33$), where children received only ORS solution for 24 hours followed by khitchri (culturally acceptable food made from rice, legumes and cottonseed oil) and half-strength cow's milk formula
- Group B ($n = 36$), where children received khitchri and half-strength cow's milk formula along with ORS solution immediately after rehydration.

The admission characteristics of the two groups were similar with regard to age, weight, vomiting, purging rate, dehydration status and nutritional status. No statistically significant differences were seen between the two groups for weight gain (at 24 hours and 72 hours post rehydration), mean stool output or the number of stools. There was also no difference between the two groups regarding number of treatment failures (children started on IVT). [EL = 1–]

A quasi-randomised study carried out in Israel⁴¹ in a primary care unit involved 90 infants aged 1–12 months with acute watery diarrhoea (duration up to 7 days) and mild dehydration. Excluded were babies younger than 30 days, children born prematurely, those receiving antibiotic therapy, those with moderate to severe dehydration and those whose parents refused to participate in the study. Allocation to the early feeding ($n = 53$) or the late feeding ($n = 37$) group was done by flipping a coin and children in both the groups were re-fed after an initial rehydration period with WHO ORS solution. In the early feeding group, children were given ORS solution for 6 hours (50 ml/kg), following which parents were advised to continue the same feeding that was being given prior to presentation and alternate it with ORS solution (75 ml/kg every 18 hours). In the late feeding group, only ORS solution was given for the initial 24 hours (200 ml/kg per day) and then feeding introduced. The two groups were similar regarding baseline demographic characteristics and clinical features on presentation. The outcomes were assessed at 24 hours and at 2 weeks but there was a high drop-out rate (11% at 24 hours and 30% at 2 weeks). There were no statistically significant differences between the two groups for any of the outcomes – percentage weight gain, state of dehydration, duration of diarrhoea or hospital admissions, at either 24 hours or at 2 weeks. [EL = 1–]

In another quasi-randomised trial, from Romania,¹²¹ 122 infants (aged 1–12 months) with acute diarrhoea (duration up to 5 days) and without signs of severe dehydration were recruited for the study. Infants with frequent episodes of vomiting, ileus or severe dehydration/shock were excluded. Children were allocated to the early feeding ($n = 73$) or late feeding ($n = 49$) group depending on the day of the week they were examined (odd or even). In the early feeding group, a non-restrictive diet was used, that is, in breastfed infants breastfeeding was continued or in non-breastfed infants a feeding regimen adapted to age was given after 3–6 hours of initial rehydration with ORS solution or rice water. The feeding regimen used prior to the onset of illness was reached within 2–3 days in this group. In the late feeding group, breastfeeding or formula feeding was discontinued for 24–36 hours and only ORS solution given for the first 6–12 hours. In the next 24 hours, carrot soup and rice water were introduced and gradually normal feeds were introduced so that the normal feeding regimen (prior to onset of illness) was resumed within 4–6 days. The baseline demographic characteristics, including the proportion of children with mild/moderate dehydration and proportion with pathogens identified in stool examination, were similar between the two groups. The mean percentage weight gain in the early feeding group was significantly higher compared with the late feeding group at 7 days ($+1.2\% \pm 1.1\%$ versus $-0.01\% \pm 0.9\%$; $P = 0.01$). Moreover, the proportion of infants with weight loss (compared with the pre-illness weight) was significantly lower in the early feeding group (6.2% versus 37.2%;

$P < 0.01$), and a significantly higher number of children in this group gained weight at 7 days compared with the late feeding group (76.6% versus 32.6%; $P = 0.01$). However, there were no statistically significant differences between the two groups regarding the frequency of stools per day, stool output during hospitalisation or duration of diarrhoea. [EL = 1–]

Evidence summary

There is a lack of quality evidence to answer the question of the benefit of early feeding compared with late feeding. Results from three studies (two RCTs and one quasi-randomised trial) suggested that weight gain was higher in children who received early feeding (with breast or cow's milk or solid foods) along with ORS solution compared with children who were started on these feeds after 1–3 days of initial rehydration. Two of these three studies found evidence of weight gain at 7 days after admission, while one study found evidence of weight gain only in the initial part of study but not at 5 days or 2 weeks after admission. The other two studies did not find any evidence of weight gain. All the studies reported no differences between the early feeding group and the late feeding group for the other outcomes – duration of diarrhoea, stool output or treatment failure.

6.2.2 Reintroduction of milk or other liquids

Evidence overview

Seven studies are included under this section – six RCTs comparing reintroduction of full-strength feeding with graded re-feeding regimens, while one RCT looked at the effect of introducing juices in the feeds of children after appropriate rehydration.

An RCT conducted in two hospitals in Guatemala and Brazil¹²² recruited 159 boys aged 15 days to 6 months with acute diarrhoea (duration less than 5 days), no visible blood in the stool and no clinical signs of severe dehydration. Almost half of the study population was malnourished. Excluded from the study were infants with severe malnutrition, who were exclusively or mostly breastfed, who had systemic infections or who had other infections requiring specific additional treatments. Children with dehydration were initially rehydrated orally with the WHO ORS solution and then randomly assigned to receive full-strength cow's milk formula from the start (Group A, $n = 80$) or the formula was reintroduced in a graded manner (half-strength for 24 hours followed by two-thirds-strength for the next 24 hours and then full-strength cow's milk formula, Group B, $n = 79$). Sealed envelopes were used for randomisation and the investigators and clinical staff were unaware of the group status. The milk formulas were prepared by a dietitian who was not involved in the clinical management or data collection, and both the formulas were given in opaque bottles (150 ml/kg per day divided in eight feedings). Maintenance therapy in the form of ORS solution and plain water was offered to the infants along with the feeds. The baseline characteristics of the two groups at the time of admission were comparable and outcomes were assessed on day 5 at the time of discharge. There were no statistically significant differences between the two groups for any of the outcomes studied: duration of diarrhoea, percentage weight gain, stool output (frequency and volume), total intake of milk and ORS solution, or treatment failure rate. However, the mean energy consumption (in kJ/kg) during the first 24 hours was significantly higher in the group of children given full-strength formula compared with the other group (310 ± 130 kJ/kg versus 172 ± 67 kJ/kg; $P < 0.05$). [EL = 1+]

An RCT from the UK¹²³ recruited 62 infants younger than 6 months admitted to a hospital with acute gastroenteritis (duration less than 7 days) and mild or moderate dehydration. Infants were excluded if the diagnosis was not thought to be gastroenteritis or if infants were already receiving low-lactose preparations for presumed lactose intolerance. After rehydration with ORS solution for 12 hours, the infants were randomly allocated to receive either full-strength re-feeding (full-strength cow's milk formula or breast milk, $n = 30$) or graded re-feeding (one-quarter-strength for 12 hours, then half-strength for 12 hours followed by full-strength formula, $n = 32$). No details were given about the process of randomisation, concealment of allocation or blinding. The two groups were similar in their baseline characteristics (age, sex, ethnic origin, weight, duration of symptoms and treatment received before admission). A total of 42% of the infants (26/62) had recurrence of diarrhoea within 7 days of re-feeding but there were no statistically significant differences between the two groups for the incidences of lactose intolerance or recurrence. The

mean percentage weight gain and the mean duration of hospital stay were also similar in the two groups. [EL = 1–]

In another RCT from UK,⁴⁹ 46 children admitted to a hospital were recruited for the study if they were aged between 6 weeks and 4 years, had diarrhoea with or without vomiting (duration less than 5 days), had less than 5% dehydration, and gastroenteritis was the only disease present. The children were randomly allocated to one of the three feeding regimens:

- re-feeding with full-strength cow's milk ($n = 16$)
- clear fluids until diarrhoea settled followed by introduction of full-strength milk ($n = 16$)
- clear fluids until diarrhoea settled, followed by graded re-feeding in increasing concentrations by a one-quarter-strength every 8 hours till full-strength achieved ($n = 14$).

Exclusion criteria were not defined and no details were provided about the process of randomisation, concealment allocation or blinding. The study only assessed length of hospital stay as an outcome, and there was no statistically significant difference between the three groups for this outcome. [EL = 1–]

In an RCT conducted in a hospital in Australia,⁴⁶ 62 infants aged above 6 months with gastroenteritis for less than 7 days but no other major illness were enrolled for the study. The initial method of rehydration was not standardised but all children were taken off their normal diet and given clear fluids either by mouth or intravenously. Following rehydration, infants were randomly allocated to the graduated re-feeding group (half-strength milk for 24 hours and then normal feeds, $n = 31$) or to immediate resumption of full-strength milk and normal food ($n = 28$). The authors did not specify the randomisation process, concealment of allocation or blinding. At the time of admission, the two groups of children were comparable regarding demographic characteristics and severity of disease. The mean weight loss during the first 24 hours was lower in the group of children receiving full-strength feeding compared with graded re-feeding group but this difference was not statistically significant (-0.02 ± 0.25 kg versus -0.14 ± 0.21 kg; $P > 0.05$). The full-strength feeding group also had a shorter stay in hospital but again the difference was not statistically significant. [EL = 1–]

Another RCT, from South Africa,¹²⁴ recruited 74 children aged between 3 and 36 months who were admitted to a hospital with acute gastroenteritis requiring IVT and who did not have severe malnutrition or lactose intolerance at the time of admission. After rehydration with IVT, the children were randomised to receive either immediate full-strength cow's milk formula re-feeding ($n = 29$) or graded re-feeding of half-strength for 24 hours, two-thirds-strength for the next 48 hours, and then full-strength cow's milk ($n = 32$). The authors did not give details about the exclusion criteria, process of randomisation, allocation concealment or blinding. About 18% of the children (13/74) dropped out of the trial owing to lactose malabsorption. The main outcome measure was duration of diarrhoea in days and there was no statistically significant difference between the two groups (2.62 versus 2.46 days; $P < 0.05$). [EL = 1–]

In an RCT in the UK,¹²⁵ 68 infants who were admitted in a hospital with acute gastroenteritis (of less than 7 days' duration) and mild or moderate dehydration were randomised to one of three re-feeding groups. Following appropriate assessment and rehydration, the infants were randomised to either immediate full-strength re-feeding with cow's milk formula, graded re-feeding (in quarter measures per 24 hours) with cow's milk formula or immediate full-strength hydrolysed whey protein formula. There were no statistically significant differences in the mean duration of hospital stay or the incidence of vomiting between all three groups. However, there was better weight gain in both the cow's milk formula groups compared with the whey formula ($P = 0.01$) and the best weight gain was in the immediate full-strength milk formula group. One-quarter of the infants randomised to the whey formula refused to feed with it. [EL = 1–]

An RCT conducted in Brazil¹²⁶ evaluated the effect of juice intake during acute diarrhoea. The trial included 90 male infants aged 4–18 months with an episode of acute diarrhoea (duration less than 3 days prior to admission) and moderate dehydration. Children presenting with severe dehydration or other conditions or concurrent serious illness, with history of chronic diarrhoea and those exclusively breastfed were excluded from the study. After treating rehydration orally with ORS solution over 6 hours, maintenance rehydration therapy was continued and infants started on their usual diet of age-appropriate milk formulas/feedings and complementary foods. As part of the usual diet, 30 infants were randomised to receive apple juice (AJ) twice daily, 30

infants were randomised to receive white grape juice (WGJ) twice daily and 30 infants were randomised to receive coloured, flavoured water (WA) twice daily. The WA was coloured and flavoured to resemble juice and the investigators were unaware of the group allocation, but the process of randomisation was not explained. Plain water was offered *ad libitum* between meals to all infants. Children in all three groups were similar in age, duration and severity of diarrhoea and presence of vomiting, and there were no differences between the groups for serum electrolyte levels or haematocrit values. Although the total energy intake was higher in the juice-fed groups compared with the water group, the duration of diarrhoea after randomisation was significantly lower in the water group compared with the juices group (49.4 ± 32.6 hours AJ group versus 47.5 ± 38.9 hours WGJ group versus 26.5 ± 27.4 hours WA group; $P < 0.05$). The mean weight gain was higher in the juice groups but the difference was not statistically significant. [EL = 1+]

Evidence summary

Six trials compared the introduction of full-strength feeding after rehydration with graded re-feeding but there were differences between the trials regarding the method of graded re-feeding and outcomes measured. Five of these trials were of poor quality (with EL = 1–) and had small sample sizes. However, the evidence was consistent in that there was no harm in giving immediate full-strength re-feeding with cow's milk formula following rehydration and also no benefit of graded re-feeding over immediate full-strength re-feeding. Two trials found evidence of increased weight gain with full-strength formula but the differences were not statistically significant.

Results from another trial with EL = 1+ suggested that giving juices to children after rehydration prolonged the duration of diarrhoea compared with water. Although children receiving juices had a higher weight gain, the difference was not statistically significant.

6.2.3 Reintroduction of solid foods

Evidence overview

There were seven RCTs that describe mixed diets. All the studies involved 100 participants or fewer (range 46–95) and focused on culture-specific foods.

Two of the RCTs were direct comparisons of two local diets.

The first RCT, conducted in Pakistan,¹²⁷ recruited 78 children aged between 6 and 36 months admitted to hospital after presenting to outpatients with a history of acute non-bloody diarrhoea of less than 7 days' duration. Children were excluded from the study if they were exclusively breastfed, had a temperature of over 102 °F, had any systemic illness (including pneumonia, meningitis or convulsions), were comatose after rehydration, had seizures, had paralytic ileus or had third-degree malnutrition (Gomez classification). Children were rehydrated if necessary with either ORS solution or IV Ringer's lactate and then randomly assigned (computer-generated sequence and allocation of treatment by drawing lots) to either the dowdo diet (wholewheat flour, cow's milk, oil, salt and water) ($n = 39$) or the khitchri diet (rice, lentils, oil, salt and water) ($n = 39$). One child from each group was later withdrawn from the study and there were three treatment failures (two in the khitchri group and one in the dowdo group). The two groups had similar characteristics at the start of the study. Outcomes were assessed over 5 days. No statistically significant differences were seen between the two diets in stool weight (males only), stool frequency, caloric consumption/kg, total weight change or duration of hospital stay. However, mothers reported that the children preferred the dowdo diet (27/36) to the khitchri diet (19/34) ($P = 0.2$) and therefore were more likely to use it at home. [EL = 1+]

The second study, conducted in Peru,¹²⁸ recruited 46 male infants aged between 6 and 24 months if they had acute diarrhoea (more than three stools per 24 hours) of less than 96 hours' duration prior to hospital admission. Children were excluded if they were breastfed more than once a day, had significant wasting, oedema or systemic illness affecting enteral feeding, or had had a diarrhoeal episode in the previous fortnight. The children were randomly assigned (fixed interval, block randomisation to allow for age and dehydration confounders) to either a rice bean diet (*Phaseolis vulgaris*, 'frijol canario', soybean oil, cotton seed oil) ($n = 25$) or rice soy diet (rice, soy protein isolate, corn syrup, soybean oil, cotton seed oil) ($n = 21$). Rehydration therapy (according to WHO guidelines) and subsequent hydration maintenance was given as necessary.

The two groups had similar characteristics at the start of the study. Five patients were considered treatment failures (two in the rice bean group and three in the rice soy group). The mean energy consumption was similar between the two groups up to day 4, but consumption was greater in the rice bean diet group compared with the rice soy diet group on day 5 (161.8 ± 17.5 kcal/kg per day versus 138.8 ± 21.0 kcal/kg per day; $P < 0.001$) and day 6 (161.8 ± 13.7 kcal/kg per day versus 144.6 ± 20.1 kcal/kg per day; $P < 0.001$). There were no differences between the two diet groups regarding the overall weight gain or length of hospital stay but the duration of diarrhoea was significantly less in the rice bean group compared with the rice soy group (60 hours versus 121 hours; $P = 0.01$). [EL = 1-]

Two of the RCTs compared the use of porridge in different consistencies.

In one Bangladeshi study,¹²⁹ infants aged 6–23 months with a history of watery diarrhoea of less than 72 hours' duration and three or more liquid stools in the 24 hours before admission were recruited. Those with systemic infections (pneumonia, bacteria or other complications) or severe malnutrition were excluded. The children were randomly assigned (using separate randomisation lists for under and over age 1 year and coded envelopes) to either amylase-treated wheat porridge ($n = 32$), unaltered thick porridge ($n = 32$) or porridge diluted with water ($n = 31$). Participants were stabilised with oral or IV rehydration therapy as necessary and a hospital milk–cereal mixture diet for 24 hours. The three groups had similar characteristics at the start of the study although overall more boys were younger than 1 year. Blinded assessors measured outcomes daily for 5 days. The mean intake of porridge and the total energy intake was greatest in the amylase-treated porridge group (ANOVA $P < 0.001$) but there were no statistically significant differences in weight change or duration of diarrhoea among the three groups. Significantly fewer children in the unaltered thick porridge group vomited at day 2 than in the amylase-treated porridge group (40.6% versus 76%; $P < 0.01$) or dilute porridge group (40.6% versus 64.5%; $P < 0.01$), but there were no further differences among groups up to day 5. [EL = 1+]

The second study¹³⁰ was conducted in Tanzania and recruited children aged 6–25 months who had been hospitalised for acute watery diarrhoea (defined as stools more watery and more frequent than usual, and for less than 14 days based on parent's history, and severe enough to require hospital admission). Unweaned children or those with a congenital or chronic condition interfering with food intake or kwashiorkor were excluded, as were children discharged after only 1 day and children requiring nasogastric feeding tubes. Rehydration therapy (according to WHO guidelines) was given as necessary before children were randomly assigned (using block randomisation lists and sealed envelopes) to feeding with either normal corn porridge ($n = 26$), amylase-digested porridge ($n = 25$) or fermented and amylase-digested porridge ($n = 24$). The three groups had similar characteristics at the start of the study. There were no statistically significant differences in duration of diarrhoea, recurrence of diarrhoea, median weight change or the need for IV rehydration therapy between the three groups at any point. There were a total of four deaths during the trial – one from pneumonia in the fermented and amylase-digested porridge group and three in the amylase-digested porridge group, where two children died of pneumonia and one from suspected septicaemia. However, the mean daily energy intake on days 1–4 was greater in the amylase-digested porridge group compared with the normal porridge group (46.0 ± 1.4 kcal/kg per day versus 32.4 ± 1.4 kcal/kg per day; $P = 0.003$). The study did not state the mother/child preference. [EL = 1+]

Three of the RCTs compared solid food with soy formula.

Infants aged 5–24 months with diarrhoea (more than three stools per day) for less than 96 hours were recruited in a trial conducted in Peru.¹³¹ Exclusion criteria were the use of antibiotics (more than one dose), breastfeeding (one feed per day), malnutrition (>2 SD below the international reference data) or a diarrhoeal episode in the previous 2 weeks. Children were randomly assigned (fixed interval, block randomisation to allow for age and dehydration confounders) to either a soy-based lactose-free formula ($n = 29$), wheat peas diet (wheat flour, pea flour, carrot flour, soybean oil, cotton seed oil, sugar) ($n = 28$) or potato milk diet (potato flour, dry whole milk, carrot flour, soybean oil, cotton seed oil, sugar) ($n = 28$). The allocation of interventions was not masked. The three groups had similar characteristics at the start of the study although the soy formula group were slightly older than the other groups. There were five treatment failures – one in the soy formula group and two each in the wheat peas diet and potato milk diet groups. There were no statistically significant differences in energy intake or weight gain between the three

groups at any point. However, there was a significant decrease in the duration of diarrhoea in the wheat peas diet and potato milk diet groups compared with the soy formula group (57 hours versus 55 hours versus 154 hours; $P = 0.005$). [EL = 1–]

The second study¹³² was conducted in Nigeria and recruited boys aged 6–24 months who had been hospitalised for acute watery diarrhoea (defined as more than three liquid stools per day, and for less than 72 hours). Those with gross faecal blood, who had received more than one dose of antibiotics, who were breastfeeding more than once a day or who were under 2 SD of the weight-for-length reference data from the US National Center for Health Statistics were excluded. ORT (according to WHO guidelines) was given as necessary for up to 8 hours before children started feeding with their assigned diet type. Children were randomly assigned (using separate block randomisation lists for under and over age 1 year) to either a maize–cow pea diet (maize flour, cowpea flour, palm oil, sugar) ($n = 35$) or a soy-based lactose-free formula ($n = 34$). The allocation of diets was not masked. Data gathered over 4 days for 69/74 children were presented. Only partial data were available for nine of these children. The two groups had broadly similar characteristics at the start of the study although compared with the maize–cow pea diet group the children receiving the soy formula were more dehydrated at admission ($P = 0.08$), had lower weight-for-age z scores ($P = 0.08$), had lower serum bicarbonate values ($P = 0.04$) and had a greater stool output during rehydration ($P = 0.01$). There were five treatment failures – two were in the maize–cow pea diet group and three in the soy formula group. The children on the soy formula consumed more on days 1–6 than the maize–cow pea diet ($P < 0.001$). The median duration of diarrhoea was significantly less in the maize–cow pea diet compared with the soy formula diet (42 hours versus 104 hours; $P < 0.001$). Mean weight change data were poorly described and data were presented in graph form only. [EL = 1–]

The third study,¹³³ conducted in Mexico, recruited male infants aged 5–36 months who had acute watery diarrhoea (defined as more than three liquid stools per day during the previous 24 hours, over a period under 96 hours) and clinical evidence of dehydration (according to WHO guidelines). Exclusion criteria were severe systemic infections (for example, pneumonia or sepsis), breastfeeding, a diarrhoeal episode in the previous 2 weeks or poor nutritional status (under 2 SD of the weight-for-length reference data from the US National Center for Health Statistics). ORT (according to WHO guidelines) and subsequent hydration maintenance was given as necessary prior to children being randomly assigned (permuted block randomisation) to either a mixed diet of rice, chicken, brown beans, carrots and vegetable oil ($n = 44$) or soy formula ($n = 45$). Lab evaluations were made at 6 and 24 hours and weight and length observations were made daily. Partial data were available for seven children who remained in the study for less than 6 days. There were six treatment failures (defined as recurrent dehydration, severe diarrhoea or prolonged high purging), all of whom were in the soy formula group ($P < 0.01$). There was a significant reduction in the median duration of diarrhoea in the mixed diet compared with the soy group (25 hours versus 67 hours; $P < 0.001$). Although, at day 1, infants were heavier in the mixed diet group than the soy group, by day 2 and up to day 6 there was no statistically significant difference in weights between the two groups. [EL = 1–]

Evidence summary

Seven RCTs were examined but only three of them were of fair quality [EL = 1+]. All the trials recruited fewer than 100 subjects and they compared a wide range of mixed diets based on rice, lentils, porridge, soy and/or maize. No single solid diet or composition of solid diet in terms of carbohydrate, protein or fat was shown to be more effective than another for the post-rehydration, maintenance phase for children with acute diarrhoea. The diets examined were specific to the various regions in the world. Although these diets conferred no advantage, they did not have any harmful effects. However, the porridge diets suggested that a thinner food consistency aids consumption and acceptability. In the studies with soy formula, the data suggested that the soy formula may prolong the duration of diarrhoea compared with solid foods.

6.2.4 The role of special milk formulas

Evidence overview

There were three RCTs that described lactose versus lactose-free cow's milk feeds and three RCTs comparing soy formula versus lactose-containing formula. One trial described soy formula in early and late re-feeding and two trials compared cow's milk formula versus a special formula.

Cow's milk formula (lactose) versus treated cow's milk formula (none or low lactose)

One trial enrolled 65 infants aged between 6 and 34 months (mean age 14.7 months) admitted to a hospital in Finland with acute gastroenteritis and mild or moderate dehydration.⁴⁸ Exclusion criteria were not presented. Following assessment and 6–10 hours' ORT, children were randomised to either a milk-containing diet ($n = 38$) or a milk-free diet ($n = 27$), and followed up for 3 days and then at an outpatient appointment 1 month later. No details of the randomisation process were given although it was stated that the allocation of interventions was not masked. The two groups had similar characteristics at the start of the study. The authors reported significantly more vomiting among the children receiving milk compared with those on a milk-free diet ($P < 0.01$). Twelve children in the milk-free diet vomited a total of 24 times compared with four children vomiting nine times in the milk-free group. There were no statistically significant differences between the two groups in the duration of diarrhoea, length of hospital stay, weight gain or episodes of diarrhoea in the following month. [EL = 1–]

One trial recruited 57 infants (age range 11–13 months) admitted to a Colombian hospital with acute diarrhoea (more than four watery stools per day with a total duration of 1 week or less) and mild or moderate dehydration.⁴² Exclusion criteria were $>50\%$ milk intake from breastfeeding, no use of lactose milk/formula prior to illness, diarrhoea caused by *Entamoeba histolytica*, antibiotic therapy in the 48 hours prior to admission chronic malabsorption syndrome or refusal of consent from parents. Children received IV and ORT and then were randomly assigned (block randomisation to allow for age and nutritional state confounders) to either a lactose-free ($n = 29$) or lactose formula ($n = 28$) group and followed up for 2 days. In both groups, following rehydration, formula was administered in half-strength for 24 hours followed by full-strength for the remaining 24 hours. The two groups had similar characteristics at the start of the study except that the duration of diarrhoea prior to admission was significantly longer in children in the lactose-free formula group (mean 3.5 days; SD 2.0 days) compared with the lactose formula group (mean 2.3 days; SD 1.0 days). There were three treatment failures – one in the lactose-free formula group and two in the lactose formula group. There were no statistically significant differences between the two groups for either of the two outcome measures – mean duration of diarrhoea and body weight increment. [EL = 1–]

Eighty male infants (age range 3–24 months) admitted to hospital with acute diarrhoea (duration less than 7 days) and mild or moderate dehydration were recruited for a trial in Thailand.¹³⁴ Children with mucous bloody stools, major systemic illness or third-degree malnutrition were excluded. Children received ORT over 4 hours and then were randomly assigned (block randomisation, coded identically packaged formula tins) to either the lactose-free ($n = 40$) or the lactose formula ($n = 40$) group following appropriate rehydration, and followed up for 7 days. These formulas were given in addition to ORS solution (after the first 4 hours) and infants were also fed rice gruel as tolerated and appropriate to age. The two groups had similar characteristics at the start of the study. There was a significant reduction in the duration of diarrhoea in the lactose-free group compared with the lactose formula group (77 hours versus 97.5 hours; $P = 0.002$) and a greater increase in the mean percentage weight in the lactose-free group at day 1 ($1.5\% \pm 1.7\%$ versus $0.3\% \pm 2.0\%$; $P = 0.003$). However, there were no statistically significant differences in weight prior to or subsequent to this period. [EL = 1–]

Soy formula versus lactose-containing formula

Fifty-eight well-nourished infants (age range 3–18 months) admitted to hospital with acute gastroenteritis and moderate or severe dehydration were enrolled in a trial in Egypt.¹³⁵ Children with shigella, salmonella and pathogenic *E. coli* were excluded. IV rehydration therapy was given prior to randomisation to either milk formula (lactose) ($n = 29$) or soy formula (lactose free) ($n = 29$). No methodological details regarding randomisation or masking were given. The follow-up period was 2–8 weeks and the main outcome measure was recurrence of diarrhoea.

On day 1 there were no cases of recurrence in either group. On day 6 there was a significantly greater number of recurrence cases in the lactose compared with the non-lactose group (52% versus 21%; $P < 0.05$). [EL = 1–]

A pragmatic comparative trial recruited 316 children (age range 3 days to 28 months) admitted to a hospital in South Africa⁴³ with acute gastroenteritis (more than three liquid or watery stools per day, and of less than 7 days' duration) and dehydration. Exclusion criteria were diarrhoea of more than 7 days' duration, ORS solution administration for 5 days prior to admission, modifications to lactose consumed in the diet or withholding of food, inability to tolerate feeds, and not having a milk/formula-based diet (older children). Children were randomised (using sealed envelopes) to one of four study groups. Following assessment and appropriate rehydration, children were randomised to either cow's milk formula ($n = 120$), breast milk ($n = 79$), breast milk plus supplementation ($n = 35$) or soy formula ($n = 75$). The main outcome measures were duration of diarrhoea and duration of diarrhoea corrected for age of child, duration of diarrhoea prior to admission, and type of infective organism, all of which showed no statistically significant differences between the four study groups. [EL = 1–]

Seventy-three infants (aged 2–12 months) with acute non-bloody diarrhoea (less than 7 days' duration) and dehydration (the majority were mild) were enrolled into a trial in a Canadian hospital.¹³⁶ Infants were excluded if they were breastfed, had been noted as intolerant to the test formulas or were malnourished. Randomisation (using a random numbers table and coded identically packaged formula) was to two treatment groups, to soy ($n = 39$) or cow's milk ($n = 44$), following appropriate rehydration within the first 24 hours. Parents were given a 14 day supply of formula and kept a diary of observations of their child until clinical examination at day 14. There were no statistically significant differences in weight gain between the two groups at 14 days or in the median duration of hospital stay (not all infants were hospitalised). However, the mean duration of diarrhoea was significantly less in the soy compared with the cow's milk group (4.5 ± 3.6 days versus 6.6 ± 4.2 days; $P < 0.01$). [EL = 1–]

Soy formula in early and late re-feeding

Early versus late feeding with a soy formula was investigated in a trial involving 56 infants aged between 2 and 12 months (mean 6 months) with acute diarrhoea (more than five watery stools in the previous 24 hours, and of less than 7 days' duration) and mild dehydration ($>7\%$ dehydration) seen in a US hospital outpatient department or a private health clinic.¹³⁷ Exclusion criteria were not presented. Following assessment, infants were randomised (using a random number tables; no allocation or masking details were provided) to either ORS solution plus soy formula for 24 hours ($n = 29$) or ORS solution and water for the first 24 hours followed by half-strength soy formula for next 24 hours and then full-strength soy formula ($n = 27$). They were then discharged and seen daily in clinic or followed at home until resolution of diarrhoea. Outcome measures were percentage resolved illness, duration of diarrhoea and percentage weight gain. The two groups had similar characteristics at the start of the study. There was a statistically significantly greater percentage of resolved illness in the early group versus the late group at the 48 hour time point (72% versus 44%; $P = 0.02$) but at the post-48 hour time point the early group showed a statistically significantly lower percentage of resolved illness compared with the late group (21% versus 56%; $P < 0.01$). The mean duration of diarrhoea was also significantly shorter in the early group compared with the late group (2.0 ± 0.2 days versus 2.7 ± 1.3 days; $P = 0.02$). However, there were no statistically significant differences in the mean weight gain between the groups at 24 hours, at resolution of illness or at 2 weeks post therapy. [EL = 1–]

Cow's milk formula versus a special formula

Sixty infants younger than 2 years (mean age 9 months) with mild acute gastroenteritis (no definition given) and no dehydration presenting to a hospital outpatient department were enrolled in a trial in India.¹³⁸ Criteria for exclusion were prior antibiotic therapy, milk elimination during current illness, concurrent non-gastrointestinal infections, gross blood in stools and moderate or severe dehydration. Infants were randomised (using block randomisation and sealed envelopes) to either milk-free formula (rice powder, mung bean powder, sugar, coconut oil) ($n = 30$) or cow's milk formula ($n = 30$) and followed up at home for at least 11 days. Trained observers visited the children's households every 3 days up until day 7 or until the child recovered. The two groups had similar characteristics at the start of the study. There were three treatment failures, two in

the milk-free group and one in the cow's milk group. There was no difference in the duration of diarrhoea between the two groups. There was a significant difference in the mean weight gain at day 4 and at recovery in favour of the cow's milk formula group ($P < 0.05$ for both). [EL = 1–]

Following admission to a hospital in Venezuela, 73 male infants (age range 3–14 months) with acute non-bloody gastroenteritis (more than four watery stools in the previous 24 hours, and of less than 96 hours' duration) and mild or moderate dehydration were recruited in a trial.¹³⁹ Criteria for exclusion were shock, malnutrition, more than two breastfeeds per day, ORT failure in the first 8 hours or other underlying disease requiring treatment at admission. The children were assessed and rehydrated appropriately over 4 hours with WHO ORS solution and then randomised (using block randomisation and sealed envelopes) to either cow's milk ($n = 37$) or an experimental soup (59% hydrolysed plantain, 27% chicken meat with skin, 14% coconut oil) ($n = 36$). The two groups had similar characteristics at the start of the study except that children in the cow's milk group had consumed significantly more water 48 hours prior to admission and had had a significantly longer duration of diarrhoea. The infants were followed up for 1 month by trained observers and the main outcome measures were duration of diarrhoea and weight increase after admission at 48 hours and at discharge. There were no differences in these outcomes between the two groups. [EL = 1–]

Evidence summary

There is lack of good-quality evidence to inform this question. Results from the included studies suggested that there was no statistically significant benefit of using a non-lactose formula (whether treated cow's milk or soy formula) over a lactose-containing formula in the re-feeding period following rehydration. There was also insufficient evidence for any other special formula to make a definitive statement. Two comparative RCTs of soy formula suggested that early compared with late re-feeding with soy formula reduced the duration of diarrhoea but had no effect on overall weight gain.

GDG translation from evidence to recommendation for Section 6.2

Early versus late re-introduction of feed

The GDG noted that studies comparing early and late reintroduction of feeding used different time scales and endpoints so that there was a lack of comparable evidence with which to answer this question.

The GDG considered that it is important to avoid malnutrition in children with gastroenteritis. Given that there was no evidence of harm with the early re-introduction of cow's milk, milk formula or solid foods, and that there was a trend towards increased weight gain in the studies identified, early re-introduction of feeding is appropriate.

Reintroduction of milk or other liquids

Historically, a common practice following rehydration in formula-fed infants has been to give diluted milk and then gradually increase the concentration to full strength (regrading). However, the available evidence shows no benefit from this approach and the GDG believes that giving full-strength formula is likely to be beneficial in terms of nutrition and weight gain.

Fruit juice is sometimes given by parents during gastroenteritis. However, the evidence suggests that this prolongs diarrhoea.

Reintroduction of solid foods

The GDG noted that certain dietary restrictions were sometimes advised in the early phase following rehydration. However, the only relevant evidence available related to a few very specific diets and no clear benefit or adverse effects were identified. The GDG agreed that reintroduction of solid foods following rehydration is to be recommended. The diet offered should be palatable and acceptable to both child and family.

The role of special milk formulas

Transient lactose intolerance is believed to occur in some children with gastroenteritis. This has led to the suggestion that lactose-free feeds may be beneficial following rehydration. The available evidence shows no benefit from such formulas in studies continued for up to 7 days.

There has also been a belief that cow's milk protein intolerance may occur following gastroenteritis, leading to the suggestion that soy-based formula may be beneficial. There was a lack of evidence of clinical benefit from the use of this formula and so the GDG considered that it should not be recommended.

Most children with gastroenteritis have diarrhoea for several days and it is important, provided weight gain is adequate, that this is recognised as a normal phenomenon. To use specialised formula feeds is unnecessary and expensive, and might cause parental concern.

Recommendation on feeding following rehydration

After rehydration:

- give full-strength milk straight away
- reintroduce the child's usual solid food
- avoid giving fruit juices and carbonated drinks until the diarrhoea has stopped.

7 Antibiotic therapy

Introduction

Gastroenteritis is most often caused by a viral enteric pathogen, and even in those with bacterial or protozoal infections the disease is generally self-limiting. Treatment has usually been recommended for dysenteric shigellosis and amoebiasis, cholera, pseudomembranous colitis, and for some other organisms in particular circumstances.¹⁴⁰ The evidence relating to the use of antibiotics in young children with gastroenteritis was reviewed with a view to making recommendations on good practice.

Clinical question

What is the role of antibiotic therapy in children with gastroenteritis?

A search for randomised trials or systematic reviews comparing antibiotic treatment with placebo or no treatment of gastroenteritis in children was performed. Of 130 citations identified, 25 were retrieved in full copy. Of these, 11 were excluded, but 14 compared use of antibiotics with placebo and were included in this review.

7.1 Salmonella

Evidence overview

Four randomised trials^{141–144} evaluated the effectiveness of antibiotic treatment compared with placebo or no treatment for children presenting to hospital with acute diarrhoea. These trials were conducted in the USA,¹⁴¹ Taiwan,¹⁴² Canada¹⁴³ and Colombia.¹⁴⁴ Three trials had three treatment arms^{141–143} and one trial¹⁴⁴ had two treatment arms but according to protocol changed the route of antibiotic administration from intramuscular (IM) to oral in the second year of the study.

The first RCT, from the USA,¹⁴¹ included children aged up to 8 years ($n = 45$) presenting at hospital with acute diarrhoea and with salmonella species subsequently isolated in rectal swab cultures. Children with a history of adverse drug reactions to penicillins, with another focus of infection or who were under 6 weeks of age were excluded. Participants were randomised to one of three treatment arms to compare the effects of ampicillin (100 mg/kg per day) ($n = 15$), amoxicillin (100 mg/kg per day) ($n = 15$) and placebo ($n = 14$) given in four equal doses daily for 5 days for the treatment of salmonella gastroenteritis. Computer-generated random number lists were used to assign the children to pre-coded drugs. Separate randomisation lists were used for children under and over 1 year of age. The main outcomes assessed were the mean days until diarrhoea stopped (diarrhoea cessation defined as the day of the first formed stool without mucus), the mean days until diarrhoea improved (defined as improved stool consistency and a decrease in the number of stools), the mean days until the first negative culture (defined as the first of at least two consecutive negative cultures), the mean days until last positive culture, bacteriological relapse and diarrhoea relapse. Outcome assessors were blind to the treatment the children received. [EL = 1–]

The groups were broadly comparable at baseline, except that children receiving amoxicillin were younger (mean age 7.7 ± 1.7 months) than those in the ampicillin (mean age 15.7 ± 5.7 months) and placebo groups (mean age 19.8 ± 7.4 months). There were no statistically significant differences between the ampicillin, amoxicillin and placebo groups for the mean number of days until diarrhoea stopped or the mean number of days until the first negative culture. Participants receiving ampicillin and amoxicillin did have a significantly reduced mean number of days until diarrhoea improved compared individually with placebo (WMD -1.20 days; 95% CI -1.65 to -0.75 days and WMD -1.00 days; 95% CI -1.45 to -0.55 days, respectively), but the difference across all three groups was not significant (Kruskal–Wallis nonparametric ANOVA $P > 0.2$). Excretion of

salmonella continued for significantly longer in the ampicillin group compared with the placebo group (days until last positive culture WMD 20.40 days; 95% CI 13.49 to 27.31 days) and the amoxicillin group compared with placebo (days until last positive culture WMD 16.10 days; 95% CI 8.75 to 23.45 days), but differences across all three groups were not statistically significant (Kruskal–Wallis nonparametric ANOVA $P > 0.5$). Eight patients in each antibiotic treatment group developed bacteriological relapse (16/30), although there were no relapses in the placebo group. This difference was statistically significant ($P = 0.003$). All but one of the relapses occurred between days 4 and 20 after entering the study. Three patients with bacteriological relapse from each antibiotic group also suffered a diarrhoeal relapse (6/30). There were no diarrhoeal relapses in the placebo group ($n = 14$), but this difference was not statistically significant.

The second three-armed study, from Taiwan,¹⁴² recruited 42 children older than 6 months presenting to hospital with suspected salmonella enteritis (defined as blood and/or mucoid diarrhoea with or without fever). Confirmation and serotyping of salmonella was performed using stool culture. Children were excluded if they had a negative salmonella stool culture, a toxic appearance, were vomiting, had abdominal distension indicative of sepsis or ileus or if they had taken antibiotics in the 72 hours prior to admission. Participants were assigned to treatment with oral azithromycin 10 mg/kg per day, in one dose daily for 5 days ($n = 14$), cefixime 10 mg/kg per day, in two doses daily for 5 days ($n = 14$) or to no treatment ($n = 14$). A computer-generated random number program was used to assign the children to treatment groups. No details of blinding of outcome assessors or of a power calculation were given. Patients returned to clinic 7 days after completing the course of treatment, and every week thereafter for stool sampling and culture, until two consecutive normal stools were noted. The main outcomes assessed were duration of diarrhoea and fever after initiation of therapy, and clinical or bacteriological relapse. [EL = 1–]

The three groups were similar at the baseline for sex and clinical parameters but children receiving cefixime were younger those in the other two groups ($P < 0.05$). No statistically significant differences were found between azithromycin or cefixime compared with each other or to no treatment for the mean duration of diarrhoea post treatment or the proportion of patients with positive cultures at week 3 post treatment.

A third three-armed treatment trial, from Canada,¹⁴³ included children aged between 10 months and 15 years who were admitted to hospital with a history of diarrhoea, fever for 3 days or more and/or mucus and blood from diarrhoeal stools. Only those with a subsequent positive culture for salmonella remained in the study. Children who had received antibiotics in the previous 5 days or who had renal or hepatic disease, blood dyscrasia, or salmonella bacteraemia were excluded. Participants were randomly assigned to treatment with 20 mg/kg per day trimethoprim plus 100 mg/kg per day sulfamethoxazole oral suspension four times per day for 7 days ($n = 14$) or ampicillin 100 mg/kg per day oral suspension or capsules four times per day for 7 days ($n = 10$) or no antibiotic treatment ($n = 12$) for the management of salmonella enteritis. No details regarding allocation concealment, sequence generation, blinding of outcome assessors or a power calculation were provided. Follow-up was by daily physical examination and culture of stool specimens, during treatment. After treatment had finished, two or three consecutive daily stool samples were taken for culture at 1 week, 8 weeks and 6 months. Family contacts also had stool cultures performed at admission and as for participants post therapy. [EL = 1–]

The treatment groups were comparable at baseline for age and clinical parameters. No statistically significant differences were noted between the trimethoprim/sulfamethoxazole, ampicillin, or no treatment groups for the mean duration of diarrhoea after start of therapy (2.8, 3.1 and 3 days, respectively), the mean duration of hospitalisation after start of therapy (5.3, 5 and 6 days, respectively) or the mean duration of fever after start of therapy (3.2, 1.6 and 2.6 days, respectively).

The fourth trial, from Colombia,¹⁴⁴ examined the effect of ampicillin versus placebo on salmonella infection. One hundred and ten of 282 malnourished infants and children younger than 2 years admitted to hospital with diarrhoea as a major symptom had salmonella isolated from culture of stool specimens. Children were recruited into the study once culture confirmation of shigella, salmonella or *E. coli* was made from rectal swab and stool specimens taken 12–16 hours previously. One patient without recognised pathogens was entered into the study for every two patients with shigella, salmonella or *E. coli*. Treatments were given intramuscularly (IM ampicillin versus IM sterile fructose) in the first year of the trial, and orally in the second (oral suspension of

100 mg/kg per day ampicillin or placebo suspension in equally divided doses every 6 hours for 5 days). Fifty-seven participants received either IM or oral ampicillin and 53 received either IM fructose or oral placebo. A random numbers list was used to assign children to treatment groups. The treatments were prepared in foils for suspension in water before use and allocation was not known to investigators, patients or outcome assessors. [EL = 1+]

The treatment groups were similar at baseline for age, sex, race, diarrhoeal duration, dehydration status, clinical examinations and prior treatment with antimicrobial or antidiarrhoeal drugs. No statistically significant differences were reported between the ampicillin and placebo groups for the mean number of days until diarrhoea improved or ceased or for the mean number of days until the patient became afebrile or culture negative. No patient receiving IM ampicillin relapsed (reversion to positive cultures after a period of negative culture) after the 5 day course of therapy. Although details of relapse in the placebo group were not presented, the authors asserted that this finding was statistically significant ($P = 0.02$) and that fewer patients receiving IM antibiotics than those receiving either placebo ($P = 0.01$) or oral ampicillin ($P = 0.04$) became short-term salmonella carriers (culture positive any time after completion of therapy).

Evidence summary

The trials included to inform this section were generally of poor quality (except for one RCT) with small sample sizes, and there was variation in the specific antibiotics used. Nevertheless, there was consistent evidence from the trials suggesting that antibiotic treatment did not shorten the duration of diarrhoea or lead to an earlier resolution of clinical symptoms. The good-quality RCT reported that IM ampicillin protected children against relapse and carriage of salmonella infection significantly better than placebo or oral ampicillin, while another trial (with EL = 1–) reported an increase in the carrier rate with oral ampicillin and amoxicillin use compared with the placebo.

7.2 Campylobacter

Evidence overview

Three RCTs were identified that compared erythromycin treatment with placebo or no treatment for campylobacter enteritis, and they were conducted in South Africa, Canada and Peru.

The first RCT, from South Africa,¹⁴⁵ examined the effect of erythromycin treatment for campylobacter-associated enteritis compared with placebo in infants aged 1–24 months. Children admitted to hospital with diarrhoea of less than 96 hours' duration and who had not received any antimicrobial therapy for this illness were included in this study ($n = 26$). Confirmation of *Campylobacter jejuni* and any other infection was from microscopic and culture examination of stool samples. Results for those children who were infected only with *Campylobacter jejuni* ($n = 8$) are presented here. Exclusion criteria details were not provided. Participants were randomised to receive an oral suspension of either 40 mg/kg per day erythromycin ($n = 4$) or placebo ($n = 4$) in divided doses for 5 days. Treatments were supplied as granules for reconstitution in pre-coded containers such that patients, investigators and outcome assessors were blind to treatment allocation. Follow-up was by daily physical and stool examination for 1 week. [EL = 1–]

Treatment groups were similar at baseline for age, sex, duration of diarrhoea, dehydration severity and weight. Although the study was well conducted, causative organisms were identified retrospectively and only eight children with *Campylobacter jejuni* infection alone were included, reducing the power of the study for these results. No statistically significant differences were found between the erythromycin and placebo groups for the mean durations of abnormal stool frequency and consistency, vomiting, dehydration or fever.

One RCT¹⁴⁶ conducted in Canada recruited children of up to 12 years of age (and their household contacts) following prospective identification of a positive, erythromycin-sensitive stool culture of campylobacter. Children with symptoms of enteritis were recalled to hospital and were allocated to no treatment ($n = 12$) or to treatment with 40 mg/kg per day erythromycin every 6 hours for 7 days ($n = 15$). Exclusion criteria were presence of other enteric pathogens in the stool, lack of symptoms and antibiotic therapy being given in the 2 weeks prior to recruitment. No

details of the randomisation process were presented, and assessors were not blinded to treatment allocation. Children were followed up until the entire household had three consecutive negative (weekly) stool samples. [EL = 1–]

The trial reported no statistically significant differences in the mean duration of diarrhoea experienced by participants receiving erythromycin or no treatment. The range in number of days with diarrhoea was 1–6 days in the erythromycin group and 1–15 days in the group receiving no treatment. A statistically significant difference was found in the mean number of days until the first negative culture between those children receiving erythromycin (2.0 ± 1.3 days) and those receiving no treatment (16.8 ± 12.5 days) ($P < 0.001$).

The third RCT, from Peru,¹⁴⁷ examined the effects of early erythromycin treatment for campylobacter-associated enteritis compared with placebo in children aged 3–60 months brought in as outpatients for treatment of acute diarrhoea ($n = 24$). Participants had five or more loose stools a day with gross blood or mucus for no longer than 5 days and had not received antibiotics for another illness. Children with clinical signs of dehydration or who were under the third percentile for weight/length ratio (US National Center for Health Statistics standard) or who had had a separate episode of diarrhoea in the previous fortnight were excluded. Participants were randomised to receive 50 mg/kg per day erythromycin oral suspension ($n = 14$) or placebo oral suspension ($n = 10$) in four doses for 5 days. Treatments were randomised and pre-coded by the manufacturers such that patients, investigators and outcome assessors were blind to treatment allocation. Allocation to treatment groups was prior to stool culture confirmation of campylobacter. Follow-up by stool culture and parental reporting of symptoms was performed for 5 days. [EL = 1+]

The mean duration of diarrhoea was significantly lower in the patients receiving erythromycin (2.4 ± 0.4 days) compared with placebo (4.2 ± 0.3 days), (WMD -1.80 days; 95% CI -2.08 to -1.52 days). However, the number of patients with normal stools at 5 days in the erythromycin group (13/14) was not significantly different from those receiving placebo (5/10) (RR 1.86; 95% CI 0.98 to 3.51). The mean number of days until last positive stool culture was significantly lower for those receiving erythromycin (0.5 ± 0.3 days) compared with the placebo group (2.2 ± 0.6 days) (WMD -1.70 days; 95% CI -2.10 to -1.30 days), but no statistically significant difference was found in the proportion of patients in each group with a positive stool culture at 5 days.

Evidence summary

Of the three available small RCTs, one trial had insufficient power to detect any statistically significant treatment differences in a small subgroup who received erythromycin or placebo for treatment of *Campylobacter jejuni* enteritis. There were conflicting results from the two remaining studies. One trial [EL = 1–] found no difference between the groups in mean duration of diarrhoea. The second trial [EL = 1+] found that the mean duration of diarrhoea was shorter with erythromycin treatment, although the ‘diarrhoeal cure’ rate at 5 days was similar between treatment groups. The difference in mean duration of diarrhoea might be explained by the second trial’s early recruitment of participants to treatment groups without awaiting stool culture confirmation of campylobacter. Thus patients would be less likely to have had long episodes of diarrhoea prior to treatment and might be more uniform in severity of illness during the study. Both studies found that erythromycin treatment demonstrated antibacterial efficacy by either reducing the mean number of days until first negative stool culture or the last positive culture. However, it could not be established in the EL = 1+ trial whether erythromycin treatment caused fewer patients to excrete campylobacter at day 5 compared with placebo.

7.3 Yersinia

Evidence overview

One RCT was identified. This study¹⁴⁸ was conducted in Canada and examined the treatment of yersinia enteritis with trimethoprim/sulfamethoxazole compared with placebo ($n = 45$). Participants were children younger than 15 years with symptomatic enteritis. Prior to recruitment, stool samples from participants had been positively cultured for yersinia. Participants and their household contacts were followed until all had three consecutive negative (weekly) stool

samples. Clinical symptoms were assessed and reported daily by a parent and stool specimens were obtained for the first 7 days, then weekly thereafter. There was about 25% loss to follow-up and results for only 34 children were presented. The mean age of children in the antibiotic group ($n = 18$) was 2.5 ± 3 years and was 3.6 ± 4.3 years in the treatment group ($n = 16$). There were no statistically significant differences between the antibiotic and placebo groups for the clinical outcomes (median duration of diarrhoea, the number of patients experiencing diarrhoea for less than 7 days, or recurrence of diarrhoea). However, statistically significant differences between the treatment groups were found for bacteriological parameters. The findings for the median number of days until 'bacteriological cure' (erythromycin median 5.5 days, range 2–53 days versus placebo, median 17.5 days, range 3–62 days; $P < 0.005$) and for the number of patients with positive stool cultures at the end of treatment (erythromycin 2/18 versus placebo 13/16; $P < 0.001$) both favoured antibiotic use. However, more participants taking antibiotics (7/18) had a bacteriological relapse compared with those taking placebo (0/16) ($P < 0.05$). [EL = 1–].

Evidence summary

Evidence from one RCT suggested that erythromycin treatment compared with placebo for yersinia gastroenteritis did not make a significant difference to clinical diarrhoeal outcomes. Although erythromycin did reduce the time taken for patients to stop excreting yersinia, its administration caused more patients to have bacteriological relapses compared with placebo.

7.4 Shigella

Evidence overview

One RCT was identified. This study¹⁴⁴ compared the effects of ampicillin with that of placebo in infants and children younger than 2 years admitted to hospital in Colombia with diarrhoea as a major symptom ($n = 282$). Children were recruited once culture confirmation of shigella, salmonella or *E. coli* was made from rectal swab and stool specimens taken 12–16 hours previously. One patient without recognised pathogens was entered into the study for every two patients with shigella, salmonella or *E. coli*. Treatments were given intramuscularly (IM ampicillin versus IM sterile fructose) in the first year of the trial, and orally in the second (oral suspension of 100 mg/kg per day ampicillin or placebo suspension in equally divided doses every 6 hours for 5 days). Overall, 37 participants had shigella infection – 16 received ampicillin and 21 received placebo. No statistically significant differences were found between the treatment groups for the diarrhoeal outcomes (mean number of days until diarrhoea improved, 2.4 versus 4.6 days, and mean number of days until diarrhoea ceased, 4.4 versus 6.8 days). IM ampicillin and the combined results for IM and oral ampicillin significantly reduced the mean number of days until the patient became afebrile, compared with the placebo (less than 0.5 versus 2.6 days; $P < 0.05$, and less than 0.5 versus 1.6 days; $P < 0.05$, respectively). Similarly, IM ampicillin and the combined results for IM and oral ampicillin significantly reduced the mean number of days until the patient became stool culture negative (0.4 versus 1.8 days; $P < 0.01$, and 0.9 versus 2 days; $P < 0.05$, respectively). IM ampicillin was found to be more effective in this respect than oral administration (0.4 versus 1.5 days; $P < 0.05$). [EL = 1+]

Evidence summary

Although the trial was well conducted, the sample size of children evaluated for this relevant section was small. The results suggested that children treated with ampicillin for shigella took fewer days to become afebrile and to stop excreting the organism than those treated with placebo. IM ampicillin was more effective than oral ampicillin in reducing the time to becoming stool culture negative, but the use of ampicillin did not reduce the time to improvement or cessation of diarrhoea.

7.5 *Escherichia coli*

Evidence overview

The Colombian trial described above¹⁴⁴ also investigated the effects of ampicillin compared with placebo on serology-confirmed enteropathogenic *E. coli* infection, as well as shigella and salmonella infections (total $n = 282$). In total, 35 of 282 infants and children younger than 2 years admitted to hospital with diarrhoea as a major symptom had *E. coli* isolated by stool culture. Of these, 18 received either IM or oral ampicillin (100 mg/kg per day in equally divided doses every 6 hours for 5 days) and 17 received either IM fructose or oral placebo in every 6 hours for 5 days. There were no statistically significant differences between either ampicillin groups, or between the ampicillin and placebo groups in the mean number of days until diarrhoea improved or ceased or in the mean number of days until the patient became afebrile or stool culture negative. [EL = 1+]

Evidence summary

Results from one trial showed no statistically significant differences between either ampicillin groups or between the ampicillin and placebo groups in the mean number of days until diarrhoea improved or ceased or in the mean number of days until the patient became afebrile or culture negative. Although this trial was of good quality, there were only 35 children evaluated to inform this question.

7.6 *Cryptosporidium*

Evidence overview

Two studies were identified for inclusion. One was a good-quality trial from Zambia but it included HIV-seropositive and malnourished children, while the other trial had methodological limitations and included both children and adults as the study population.

An RCT¹⁴⁹ conducted in Zambia recruited children ($n = 100$) who were admitted to hospital with diarrhoea, who had *Cryptosporidium parvum* oocytes identified from a pre-enrolment stool sample and whose parents consented to the child having an HIV test. All children were stabilised with fluid therapy, antibiotics and mineral supplementation as required throughout the study. Exclusion criteria were age under 1 year and receipt of a drug with antiprotozoal activity within 2 weeks of enrolment to the study. Following stratification by HIV status ($n = 50$ in each group), children were randomly assigned using a computer-generated random number list to treatment with 20 g/l nitazoxanide ($n = 25$) or placebo ($n = 25$) oral suspension (5 ml twice daily for three consecutive days). The patients and outcome assessors were not aware of the treatment allocation. The children were followed up in hospital for 8 days. The main outcomes were the clinical response on day 7 (well or continuing illness), the parasitological response, the time from first treatment to last unformed stool, and mortality by day 8. Results are presented here for the HIV-seronegative subgroup only ($n = 50$). [EL 1+]

Twenty-five HIV-seronegative children were allocated to each treatment group, although three from the placebo group were subsequently excluded as no *Cryptosporidium parvum* oocytes were detected in their stool at baseline. The groups were similar for sex, age, weight, malnutrition status, laboratory abnormalities and stool frequency. Children receiving placebo had a shorter mean duration of diarrhoea prior to enrolment than the nitazoxanide group, but this reflected one child in the nitazoxanide group reporting 91 days of diarrhoea prior to enrolment. Eleven children in each group had physical signs of malnutrition. Oedema indicative of kwashiorkor or marasmic kwashiorkor was detected in 22 children (10/25 nitazoxanide, 12/22 placebo).

Fourteen of 25 children receiving nitazoxanide were 'well' (rather than having 'continuing illness') at day 7 compared with five of 22 of those receiving placebo. 'Well' was defined as having no symptoms, no watery stools and no more than two soft stools within the previous 48 hours. 'Continuing illness' was defined as not fulfilling the definition of 'well'. This difference was statistically significant ($P = 0.037$). At day 7, significantly more children in the nitazoxanide group (13/25) had a parasitological response (defined as two negative stool examinations) compared with the placebo group (3/22) ($P = 0.007$). There were no deaths in the nitazoxanide group but

four children in the placebo group died, three from persistent diarrhoea with septicaemia and one who additionally had congestive heart failure (re-feeding syndrome). This difference was statistically significant ($P = 0.041$).

A comparative trial¹⁵⁰ conducted in Egypt was identified that examined the effect of nitazoxanide and co-trimoxazole compared with placebo for clinical and microbiological 'cure' of cryptosporidium infection. This trial was poorly reported, with no details regarding the methods used or the baseline comparability of the treatment groups. Consequently, it was considered to be potentially highly biased. [EL = 1-]

Of 1087 patients with diarrhoea examined in the outpatient clinic, 150 were found to have cryptosporidiosis. This was confirmed by two stool diagnostic tests (Ziehl–Neelsen stain and direct immunofluorescent technique). Of these 150 patients, 73 were children. Adults and children were divided into three treatment groups (nitazoxanide, co-trimoxazole or placebo) and were followed for up to 10 days. Clinical cure was not defined in the study. Microbiological cure was defined as two consecutive negative stool samples. Results of numbers of patients 'cured' were presented, although it was not clear which 'cure' was measured and when measurements were taken – microbiological cure by the 10th day was presumed. There was a statistically significant difference in the number of children cured (21/24) following administration of nitazoxanide compared with placebo (9/25) (RR 2.43; 95% CI 1.41 to 4.19; $P = 0.001$). A statistically significant difference was not demonstrated for the comparison of co-trimoxazole (8/24) versus placebo (RR 0.93; 95% CI 0.43 to 2.00; $P = 0.84$).

Evidence summary

A good-quality RCT conducted in a population of malnourished children showed that nitazoxanide was effective in achieving a clinical and parasitological response to treatment, and in preventing deaths. Results from the other, potentially biased, controlled trial suggested that nitazoxanide but not co-trimoxazole was effective in achieving a microbiological cure in children younger than 12 years with diarrhoea of cryptosporidium infection.

7.7 Treatment without prior identification of a pathogen

Evidence overview

Four RCTs were identified as relevant: two studies were conducted in South Africa^{151,152} and two in Mexico.^{153,154} Data from 378 children (aged 2 months to 7 years) suffering from gastroenteritis were collected across the four studies. Three trials had two treatment arms^{151–153} and one trial had three treatment arms.¹⁵⁴ The proportion of patients randomised but lost to follow-up was reported in all the studies (less than 20%). None of the trials included a sample size power calculation.

A trial conducted in South Africa¹⁵¹ compared the effect of trimethoprim/sulphonamide with placebo for the treatment of gastroenteritis. Children aged 5–30 months admitted to hospital for gastroenteritis ($n = 34$) were randomised into two treatment arms. There were 18 participants in one group and 26 in the other, although the authors did not specify which group received which treatment. No details of the randomisation process were given, but the investigators, patients and outcome assessors were blinded to treatment allocation. At baseline, the treatment groups were similar for age. No statistically significant differences were found between the two groups for the mean duration (in days) of diarrhoea, vomiting, pyrexia or hospital stay. [EL = 1-]

The second trial from South Africa¹⁵² examined the effect of erythromycin compared with placebo for the treatment of non-specific gastroenteritis. Included in the study were children aged 1 month to 2 years who had been admitted to a hospital with a history of diarrhoea not exceeding 96 hours and who had received no antimicrobial therapy for the illness ($n = 78$). Participants were randomised into two treatment groups and received either erythromycin oral suspension 40 mg/kg per day in divided doses for 5 days ($n = 39$) or placebo oral suspension ($n = 39$). Follow-up was by daily examination for 7 days. Treatments for the trial were supplied by the manufacturer as granules for reconstitution in pre-randomised and coded containers. The patients and the outcome assessors were blind to treatment allocation. The comparability of the groups at study entry was adequate. The distribution of pathogens was similar between

groups and results were presented for 32 antibiotic and 33 placebo recipients. There were no statistically significant differences between the two groups in the mean duration of abnormal stool frequency, vomiting, dehydration or fever. However, the erythromycin group had a statistically significantly shorter mean duration of abnormal stool consistency compared with the placebo group (WMD -0.80 days; 95% CI -1.46 to -0.14 days). [EL = 1+]

A third RCT, conducted in Mexico,¹⁵⁴ with three treatment arms compared the effects of furazolidone, trimethoprim/sulfamethoxazole and no antibiotic treatment for acute invasive diarrhoea in children. Patients aged 2–59 months brought to hospital and seen in outpatients with three or more watery stools in the previous 24 hours, with up to 5 days of diarrhoea prior to admission, and with presence of polymorphonuclear (PMN) leucocytes and blood in stool ($n = 125$) were included in the study. Patients who had received antimicrobials or antidiarrhoeal drugs in the previous 48 hours, who had amoeba in their stools, who had any concomitant disease or who had allergy or intolerance to the study drugs were excluded. Following a complete physical examination and submission of a stool specimen, participants were randomised to receive 7.5 mg/kg per day furazolidone in four equal doses a day for 5 days ($n = 42$), 8 mg/kg per day trimethoprim + 40 mg/kg per day sulfamethoxazole in two equal doses a day for 5 days ($n = 52$) or no treatment ($n = 24$). Participants were followed up with daily visits as outpatients to hospital, clinical assessment at day 3 and stool samples taken at days 1 and 6. Treatment success for participants with an identified pathogen was defined as clinical cure (absence of diarrhoea and alleviation of all symptoms) at day 3 and bacteriological cure (negative stool culture) at day 6. For patients with negative culture, treatment success was defined as clinical cure (absence of diarrhoea and alleviation of symptoms) at day 3. The methods of randomisation were not reported and it was unclear as to whether patients or outcome assessors were blinded to treatment. [EL = 1–]

At baseline, patients were similar for age, sex, weight, height, body temperature and mean stools passed per day. However, those children receiving furazolidone had fewer days with diarrhoea prior to recruitment compared with patients receiving either trimethoprim/sulfamethoxazole or no antibiotic treatment ($P < 0.02$). A statistically significantly higher number of patients (who took antibiotics) were clinically cured by day 3 compared with the no antibiotic group (furazolidone RR 1.93; 95% CI 1.21 to 3.09, trimethoprim/sulfamethoxazole RR 1.82; 95% CI 1.13 to 2.92, and for both antibiotics together RR 1.87; 95% CI 1.18 to 2.98). Similar results were seen for clinical cure rate by day 6 (furazolidone RR 2.78; 95% CI 1.25 to 6.19, trimethoprim/sulfamethoxazole RR 3.05; 95% CI 1.38 to 6.72, and for both antibiotics together RR 2.92; 95% CI 1.33 to 6.39).

However, among those patients who had negative stool cultures, there were no statistically significant differences in the proportion of patients who had been clinically cured at day 3, for either furazolidone or trimethoprim/sulfamethoxazole individually or for both antibiotics together compared with no antibiotic treatment. For patients with positive stool cultures, bacteriological cure at day 6 was only statistically significantly different from placebo when data for antibiotics were combined (RR 2.33; 95% CI 1.04 to 5.25). No statistically significant differences were found for furazolidone (RR 1.76; 95% CI 0.76 to 4.12) or trimethoprim/sulfamethoxazole (RR 1.97; 95% CI 0.85 to 4.56) alone compared with placebo.

Another RCT from Mexico¹⁵³ recruited children aged 3–84 months seen in hospital with diarrhoea into a treatment trial of trimethoprim/sulfamethoxazole compared with placebo. Participants had passed three or more unformed stools in the previous 24 hours, had less than 72 hours' duration of diarrhoea, no antibiotic treatment in the previous 7 days and were not severely dehydrated ($n = 141$) and were randomised into two treatment groups to receive 10 mg/kg per day trimethoprim + 50 mg/kg per day sulfamethoxazole oral suspension in two divided doses a day for 5 days ($n = 73$) or placebo oral suspension ($n = 68$). Daily assessments were made throughout the duration of treatment and once more at 2 weeks. Although details of the randomisation process were not reported, patients and outcome assessors were blind to treatment allocation. The groups were similar at study entry for age, pre-study diarrhoea duration, mean stool passage at 24 hours pre-therapy, fever, dehydration status and faecal leucocytes. Fifty of 141 participants had body weight under the third percentile for age according to Mexican standard criteria. [EL = 1–]

The mean time to last diarrhoeal stool was statistically significantly shorter with antibiotic use compared with placebo in all patients (58.2 versus 75.5 hours; $P = 0.021$), those with fever (58.2 versus 75.5 hours; $P = 0.021$) and those with faecal leucocytes (>3 /HPF) (57.7 versus

106.5 hours; $P = 0.025$). However, there were no statistically significant differences between the antibiotic and placebo groups for the mean number of unformed stools in a 5 day period and in week 1 and week 2 post treatment for all patients and the subgroups (those with fever and patients with $>3/\text{HPF}$).

Evidence summary

Four clinical trials performed in South Africa and Mexico examined the use of antibiotics in children presenting with diarrhoea in whom the results of stool microbiological investigations were not yet available to inform management. Only one trial was of good quality and its results suggested that erythromycin treatment reduced the mean duration of abnormal stool consistency. The other three trials had methodological limitations, evaluated different antibiotics and reported contrasting results. While one small trial reported that the use of trimethoprim/sulphonamide had no effect on duration of clinical symptoms (diarrhoea, vomiting or pyrexia) or on the length of hospital stay, another trial found evidence that this drug reduced the duration but not the severity of diarrhoea in the first 5 days of treatment. A fourth trial reported that furazolidone and trimethoprim/sulfamethoxazole achieved a 'clinical cure' in all patients within 3 days of starting treatment. This effect was not seen for patients who were subsequently found to have negative stool cultures. A protective effect of antibiotic administration was only seen for patients with positive stool cultures when the data for both antibiotics were combined.

7.8 Traveller's diarrhoea

Evidence overview

No trials including children were identified but a Cochrane systematic review of antibiotic treatment for traveller's diarrhoea in adults was found.¹⁵⁵ [EL = 1+] The authors included all trials in any language in which travellers older than 5 years were randomly allocated to antibiotic treatment for acute non-bloody diarrhoea and where the causative organism was not known at the time of treatment allocation. Patients with acute bloody diarrhoea for longer than 14 days were excluded. Twelve trials were included in the Cochrane review in total, but only nine trials that compared antibiotic therapy with placebo were relevant to this guideline ($n = 1174$). Participants were students, soldiers, tourists, hotel guests or volunteers who had travelled to Mexico (five trials), Morocco (one trial), the Gambia (one trial), Belize (one trial) and unspecified developing countries (one trial). The antibiotics used in the trials were ofloxacin, bicozamycin, ciprofloxacin (two trials), trimethoprim and trimethoprim-sulfamethoxazole, norfloxacin (two trials), fleroxacin and aztreonam. Although all nine trials reported the mean duration of diarrhoea (assessed by time to last unformed stool), only three reported the mean and standard deviation and one trial reported the mean and P value from which a pooled standard deviation was derived.

Four comparisons of antibiotic ($n = 199$) with placebo ($n = 264$) were made in three trials and statistically significant reductions in the mean duration of diarrhoea were found in those receiving antibiotics (WMD -25.86 hours; 95% CI -32.58 to -19.14 hours). One study reported a mean duration of diarrhoea of 26 hours in the antibiotic group ($n = 8$) compared with 60 hours in the placebo group ($n = 9$) (pooled SD = 28 hours)

Six trials reported the number of patients cured at 72 hours. There were statistically significantly more in the antibiotic groups who were cured at 72 hours (330/391) compared with the placebo groups (154/306) (OR 5.90; 95% CI 4.06 to 8.57).

Change of severity of diarrhoea (number of unformed stools per 24 hour period) over 72 hours was reported by two trials. There was a small but statistically significant reduction for those receiving antibiotics ($n = 117$) compared with those receiving placebo ($n = 106$) sustained over 72 hours (0–24 hours WMD -1.59 ; 95% CI -2.66 to -0.52 , 25–48 hours WMD -2.10 ; 95% CI -2.78 to -1.42 , and 49–72 hours WMD -1.38 ; 95% CI -1.94 to -0.82).

Five studies reported side effects from treatment: 110/523 participants receiving antibiotics experienced a side effect compared with only 38/339 in the placebo groups (OR 2.37; 95% CI 1.50 to 3.75) although these were said not to have been clinically serious or to have resolved on withdrawal of the treatment.

Evidence summary

No evidence in children younger than 5 years was identified. However, results from a systematic review found that antibiotic treatment was effective in reducing the duration and severity of diarrhoea in adult patients with traveller's diarrhoea, although there was an increased incidence of side effects.

7.9 Groups for whom antibiotic treatment may be indicated

Clinical question

Are there any particular circumstances where antibiotics should be given?

Evidence overview

Searches were conducted for observational studies and 203 references were returned. On the basis of the titles and abstracts, 33 were retrieved in full copy for further examination. Of these, four studies were included here.

7.9.1 *E. coli* O157:H7

Two relevant studies were identified with regard to this pathogen, which is the main cause of haemolytic uraemic syndrome (HUS).

One prospective cohort study¹⁵⁶ conducted in the USA investigated whether antibiotic treatment affected the risk of HUS in children. [EL = 2+] In total, 71 children younger than 10 years who had diarrhoea caused by *E. coli* O157:H7 were recruited to the study. Stool culture was obtained within the first 7 days of illness. On confirmation of *E. coli* O157:H7, investigators sought consent and recruited the infected child to the study. A questionnaire was administered to caregivers to record previous and ongoing clinical signs and symptoms, prescription and other medications taken (for example antibiotics and antimotility drugs). Prescription of medications was at the discretion of each physician and was confirmed retrospectively from notes. Only the initial temperature readings and laboratory test results were used for analysis. Daily blood counts and renal function tests were performed until HUS developed and resolved or until diarrhoea resolved. Multivariate regression analysis was used to evaluate the risk of HUS after adjustment for two risk factors that had been previously reported to be associated with it – the initial white cell count and the day of illness on which initial stool culture is taken. The two groups of children – those who received antibiotics ($n = 9$) and those who did not ($n = 62$) – were similar for demographic characteristics, clinical and laboratory parameters at the baseline. Overall, 10/71 (14%) developed HUS. Of the nine children who received antibiotics, five (56%) subsequently developed HUS while of the 62 who did not receive antibiotics, five (8%) developed HUS. This difference was statistically significant ($P = 0.001$) and remained so after adjustment, although confidence intervals were wide and the lower estimate was close to unity. (Antibiotics given within the first 7 days after onset RR 17.3; 95% CI 2.2 to 137; $P = 0.007$, and within the first 3 days after onset RR 32.3; 95% CI 1.4 to 737; $P = 0.03$). A statistically significant linear trend was observed for initial white blood cell count and development of HUS ($P = 0.005$). This remained statistically significant after reanalysis as a continuous outcome and adjustment (adjusted RR 1.5; 95% CI 1.1 to 2.1; $P = 0.02$). A statistically significant linear trend was also observed for the difference in HUS development according to the day that stool culture was taken ($P = 0.01$). This remained statistically significant after adjustment (adjusted RR 0.3; 95% CI 0.1 to 0.7; $P = 0.008$).

A retrospective cohort study,¹⁵⁷ also conducted in the USA, evaluated risk factors for progression of *E. coli* O157:H7 to the development of HUS. [EL = 2+] Participants were younger than 16 years, resided in Washington state and either had symptomatic, culture-proven *E. coli* O157:H7 infection or had developed HUS in January or February 1993 (during an *E. coli* O157:H7 outbreak from a 'fast food outlet' chain. Demographic, symptomatic and medication data were gathered from three sources: two telephone questionnaires administered to participants' parents (within 2 weeks of illness onset and 2–4 months later) and from examination of patients' medical records. Cases and controls were similar for age, sex and annual family income at baseline. The median age of

participants was 6 years (range 0–15 years). In total, 33/278 patients developed complete HUS and 4/278 developed incomplete HUS. There were three fatalities.

Children who reportedly vomited (29/153) were statistically significantly more likely to develop HUS than those who had not vomited (8/125) (RR 3.0; 95% CI 1.4 to 6.2). Although more children who had bloody diarrhoea or fever developed HUS, these differences were not statistically significant (RR 2.0; 95% CI 0.5 to 7.7, and RR 1.8; 95% CI 0.8 to 4.1, respectively).

To investigate early predictors, the risk of HUS was evaluated according to clinical outcomes measured within the first 3 days of illness. Vomiting remained a statistically significant risk factor in this time interval (RR 1.9; 95% CI 1.0 to 3.5) and the association was modified by age. Vomiting in children younger than 5.5 years was strongly associated with HUS development (RR 3.5; 95% CI 1.4 to 9.4), but the association was not evident in children older than 5.5 years (RR 1.0; 95% CI 0.4 to 2.4).

The use of medications was also analysed. In total, 50 children received a range of antibiotics in the first 3 days of illness. These children were more likely to live in a household with annual income over \$29,000 (RR 1.7; 95% CI 1.0 to 2.8). Eight of these children went on to develop HUS compared with 28/218 who did not receive antibiotics ($P = 0.56$). In total, 31 children received antimotility agents in the first 3 days of illness. Six went on to develop HUS, compared with 20/234 who received no antimotility treatments ($P = 0.10$). There was no statistically significant difference in the development of HUS in children who received adsorbant and antimotility drugs compared with those who did not ($P = 0.26$).

There were no statistically significant associations between HUS development and haematocrit, platelet count, blood urea nitrogen, segmented neutrophils count or band forms at presentation. However, children who had a white blood cell count of over 10 500 per microlitre were at increased risk of developing HUS (RR 5.2; 95% CI 1.6 to 17.0; $P < 0.01$), and for those with a white blood cell count of over 13 000 per microlitre this risk was larger (RR 7.2; 95% CI 2.8 to 18.5; $P < 0.01$).

Evidence summary

There was consistent evidence from two studies that a raised white blood cell count in children with *E. coli* O157:H7 was a risk factor for the subsequent development of HUS. In one study, vomiting in children younger than 5.5 years was strongly associated with the risk of developing HUS. However, there was conflicting evidence on the effect of antimicrobials. One study reported that antimicrobial treatment was an independent risk factor for HUS but the study lacked precision for this finding. The second study did not find treatment with antimicrobials or with antimotility agents (with or without adsorbant agents) was associated with increased risk of HUS.

7.9.2 Salmonella

One retrospective review¹⁵⁸ conducted in Malaysia sought to characterise the incidence, risk factors and outcome of invasive non-typhoid salmonella gastroenteritis in children aged between 1 month and 14 years. [EL = 2+]. Participants were 131 children with positive stool cultures for salmonella species but no second enteropathogen, seen in an outpatient department. Of these, 67% of children were younger than 1 year. Demographic, clinical (diarrhoea, vomiting, fever, hydration status), blood and stool outcome measures were recorded from case notes and examined. Overall, 124 children were found to have non-invasive salmonellosis and seven had invasive complications (five bacteraemia, two meningitis). Three risk factors were identified for the development of invasive salmonellosis. In total, 45 (85%) of the 124 with non-invasive disease were younger than 6 months compared with six of the seven with invasive disease ($P < 0.01$). Only 53 of those in the non-invasive group had a temperature of over 38 °C, compared with all seven of the invasive group ($P < 0.003$). Dehydration was found in five of the seven with invasive complications, but in only 25 of the 124 with non-invasive disease. One infant with bacteraemia died while awaiting a blood culture result. The authors suggested that empirical antibiotic treatment should be given to infants younger than 6 months who are febrile and dehydrated.

Another retrospective review,¹⁵⁹ conducted in Hong Kong, included 126 children with salmonella ($n = 86$), rotavirus ($n = 55$) or unspecified gastroenteritis ($n = 126$) who were admitted to hospital. [EL = 2+]. Demographic, clinical (dehydration, vomiting, fever, diarrhoea, abdominal pain), stool and medication outcomes were collected from case notes and analysed according to gastroenteritis type. Patients with salmonella were more likely to have bloody (OR 6.1; 95% CI 3.2 to 11.7; $P < 0.0001$) or mucoid stools (OR 4.8; 95% CI 2.6 to 8.9; $P < 0.001$) compared with the combined rotavirus/non-specified gastroenteritis groups. They were statistically significantly younger (median 7.1 months versus 14.6 months; $P < 0.0001$), had a longer stay in hospital (median 3.4 days versus 2 days; $P < 0.0001$), passed more stools per day (median 6.2 versus 4.2; $P < 0.0001$) and more of them experienced fever during their admission (OR 3.6; 95% CI 1.6 to 8.4; $P = 0.001$). Additionally, patients with salmonella were statistically significantly more likely to have been given antibiotics than children in the other two groups (OR 3.6; 95% CI 1.9 to 6.9; $P < 0.0001$), although administration of antibiotics was not dependent on age.

Evidence summary

Compared with other enteropathogens, salmonella gastroenteritis has repeatedly been shown to particularly affect younger children. A retrospective review from Malaysia found that 67% of all salmonella-infected children were younger than 1 year. Most children developing invasive salmonellosis (bacteraemia or meningitis) were younger than 6 months. Similarly, a study from Hong Kong found the median age to be 7.05 months (range 3.9 to 13.6 months). Fever was a significant characteristic in both studies, compared with other pathogens and as an indication of invasive salmonellosis.

Dehydration was statistically significantly associated with more severe disease in one study. Diarrhoea was more frequent in salmonella infection and stools were characteristically bloody and/or mucoid, although blood in stools was not found to be indicative of invasive salmonellosis. Vomiting was less frequent than with viral infection. Children with salmonella had longer hospital stays and were more likely to be treated with antibiotics regardless of age.

GDG translation from evidence to recommendations

The GDG recognised that gastroenteritis in children in the UK is usually a self-limiting illness that does not require antibiotic treatment. Most cases are due to viral enteric pathogens. Even with the more common non-viral pathogens, treatment is usually not indicated in the UK (see below). Antibiotic treatment is associated with a risk of adverse effects, and is a very common cause of diarrhoea.

In most cases of childhood gastroenteritis, the healthcare professional will not know the causative agent. Stool microbiological investigations are performed in selected cases only (see Chapter 3). If a bacterial pathogen is identified by stool culture, the result would not be available at the time of first presentation.

The recommendations below took into account the experience of the GDG and of the advisers, and the limitations of the studies identified (not UK-based and with few children in the study populations).

The GDG was aware of studies conducted in South Africa and Mexico several decades ago in which antibiotic therapy was administered while awaiting the results of stool microbiological investigations. There was some evidence that at that time in those studies empirical treatment had some apparent benefit. However, the GDG did not consider that those studies were relevant to the current UK setting.

The spectrum of pathogens commonly responsible for gastroenteritis in the UK is such that benefit from empirical antibiotic treatment would be highly unlikely.

Recommendations regarding the treatment of specific enteric pathogens were also considered.

A series of randomised controlled trials found little evidence of clinical benefit from antibiotic treatment for children with salmonella gastroenteritis. Indeed, there was evidence to suggest that treatment might increase the risk of salmonella carriage. The GDG therefore concluded that

antibiotic treatment should not routinely be given in salmonella gastroenteritis. However, there are some individuals at increased risk of systemic sepsis. Young infants are at increased risk of developing salmonella gastroenteritis, and those younger than 6 months are at increased risk of systemic spread. Others likely to be at high risk of sepsis are those with immune deficiency states including HIV/AIDS and malnourished infants and children. The GDG concluded that in such cases antibiotic treatment should be recommended.

The efficacy of antibiotic therapy for patients with campylobacter spp. is somewhat uncertain. One randomised controlled trial in which treatment with erythromycin began while culture results were pending found that treatment was associated with a shortened mean duration of diarrhoea. There was no evidence to suggest that antibiotic therapy was beneficial in those whose treatment began after a positive culture was available. The GDG therefore concluded that antibiotics should only be used where septicaemia is suspected.

There was no evidence that antibiotic therapy was beneficial in the treatment of yersinia enteritis. The GDG considered that antibiotics should be reserved for those with suspected or confirmed yersinia septicaemia.

The GDG was aware that there was evidence to support the efficacy of antibiotic therapy in patients with dysenteric shigellosis in adults. One randomised controlled trial of antibiotic therapy for bacterial gastroenteritis in children found that, although there was no benefit in relation to diarrhoea, the duration of fever and the time to clearance of stool pathogens were reduced. The GDG therefore concluded that those with dysenteric shigellosis should receive antibiotic treatment.

The GDG was aware that antibiotic treatment was effective in adults with enterotoxigenic *E. coli*, a very common cause of traveller's diarrhoea. The effect of antibiotic treatment for enteropathogenic and enteroinvasive *E. coli* is uncertain.

Two studies were available regarding antibiotic treatment for the protozoal pathogen *Cryptosporidium parvum*. Both evaluated the broad-spectrum antibiotic nitazoxanide that has activity against protozoa. Both reported some evidence of benefit, but these studies had methodological limitations. Routine treatment of gastroenteritis due to cryptosporidium was therefore not recommended.

Young children with *E. coli* O157:H7 appeared to have a risk of 10–15% of developing HUS. There was evidence to suggest that those with a leucocytosis at presentation are at higher risk. Vomiting, especially in children younger than 5 years, was also associated with an increased likelihood of progression to HUS. There was some evidence that antibiotic treatment might have been a risk factor for HUS, although this finding was not consistent between studies. It might be that this reported observation can be explained by the administration of antibiotics to those with more severe disease. Nevertheless, the GDG considered that there was insufficient evidence to recommend antibiotic treatment for *E. coli* O157:H7.

The GDG recognised that a number of other potential enteric pathogens exist that could cause gastroenteritis, but there were no available clinical trials on treatment in children. *Clostridium difficile*-associated pseudomembranous colitis is normally treated with antibiotics. The same is true of *Vibrio cholerae*. Protozoal infections – including *Isospora belli*, *Cyclospora cayetanensis*, *Entamoeba histolytica* and *Giardia lamblia* might all respond to antibiotic therapy, based on studies in adults.

There was no clinic trial evidence on the treatment of traveller's diarrhoea in children, but the GDG considered that trials in adult patients were relevant, and these showed evidence of benefit from antibiotic treatment. It was therefore agreed that in such cases consideration should be given to seeking specialist advice regarding antibiotic treatment in children presenting with acute diarrhoea shortly after return from overseas travel.

Recommendations on antibiotic therapy

Do not routinely give antibiotics to children with gastroenteritis.

Give antibiotic treatment to all children:

- with suspected or confirmed septicaemia
- with extra-intestinal spread of bacterial infection
- younger than 6 months with salmonella gastroenteritis
- who are malnourished or immunocompromised with salmonella gastroenteritis
- with *Clostridium difficile*-associated pseudomembranous enterocolitis, giardiasis, dysenteric shigellosis, dysenteric amoebiasis or cholera.

For children who have recently been abroad, seek specialist advice about antibiotic therapy.

8 Other therapies

Introduction

A range of other therapies have been proposed for use in gastroenteritis. These have focused on alleviating vomiting and diarrhoea. They have included a range of anti-emetic and antidiarrhoeal agents. Benefits have also been attributed to certain micronutrients and dietary fibre. In recent years there has been considerable interest in the possible role of probiotics.

Clinical question

Which interventions (other than fluid therapy and antibiotic treatment) are effective and safe?

Various medical interventions were considered under the following category headings:

1. anti-emetics
2. antidiarrhoeals
3. micronutrients and fibre
4. alternative and complementary therapies
5. probiotics.

A search was performed with no restrictions on date and this returned 1245 references. The titles and abstracts of these were appraised and 163 papers were identified as potentially relevant to the guideline and were obtained in full copy. Of these, 33 were relevant and were included in this chapter. A further two papers were identified from updating searches.^{160,161}

8.1 Anti-emetics

Many children with gastroenteritis experience vomiting, particularly in the early phase of the illness. This is a distressing symptom. Importantly, it is a major factor in leading to failure of ORT. If vomiting could be treated effectively then there might be a reduction in the use of IVT. Various anti-emetic agents have been used to prevent or reduce vomiting in children with gastroenteritis.

The phenothiazines are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. They are used to prevent or treat vomiting associated with drugs such as opioids, general anaesthetics and cytotoxics. Unfortunately, severe dystonic reactions sometimes occur with phenothiazines, especially in children. Metoclopramide is an effective anti-emetic and its activity closely resembles that of the phenothiazines. Metoclopramide also acts directly on the gastrointestinal tract and it may be more effective than the phenothiazines for vomiting associated with gastroduodenal disease.¹⁶² As with the phenothiazines, metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young. Ondansetron is a specific 5HT₃ antagonist which blocks 5HT₃ receptors in the gastrointestinal tract and in the central nervous system. It has been shown to be effective in the treatment of vomiting in patients receiving cytotoxic agents for cancer. Dexamethasone also has anti-emetic effects and is used to prevent vomiting associated with cancer chemotherapy. In this context it may be used alone or with other anti-emetics such as metoclopramide or a 5HT₃ antagonist.

Evidence overview

Five trials were identified as relevant to this review.^{160,161,163–165}

Four of these were conducted in the USA^{160,161,163,164} and one in Venezuela.¹⁶⁵ Two trials had three treatment arms^{161,165} and the rest had two. Across the five studies, data from 639 children (aged 6 months to 12 years) suffering from gastroenteritis were collected. The following comparisons were investigated:

- oral ondansetron versus placebo
- IV ondansetron versus placebo

- IV metoclopramide versus placebo
- IV dexamethasone versus placebo.

The outcomes considered were duration of the disease (vomiting and diarrhoea outcomes), tolerance of ORT, need for IVT, dehydration status and hospitalisation. Follow-up, treatment protocol and definition criteria for inclusion of the children with gastroenteritis varied between the three studies.

The first of the trials conducted in the USA¹⁶⁴ had two treatment arms and recruited children aged 6 months to 12 years with gastroenteritis presenting to a paediatric emergency department with at least five episodes of vomiting in the preceding 24 hours and who had not received an anti-emetic ($n = 145$). Those with an underlying chronic condition, possible appendicitis, a urinary tract infection or who had severe gastroenteritis requiring immediate IV fluids were excluded. Children were randomised to treatment with three doses (appropriate for age group) of oral ondansetron ($n = 74$) or placebo ($n = 71$) per day. The methods of randomisation were adequate and patients and outcome assessors were blind to treatment allocation. The power calculation presented estimated that for a treatment success rate of 80% in the ondansetron group and 60% in the placebo group, a sample size of 91 per group would be required. Outcomes measured were cessation of vomiting during the stay in the emergency department, the need for IV rehydration, hospitalisation and diarrhoeal episodes during follow-up. [EL = 1+]

The groups were similar at baseline for age, sex and severity of illness. No children were lost to follow-up in the emergency department stay, but by 48 hours 32/145 had been lost. More children in the ondansetron group (64/74) stopped vomiting in the first few hours after treatment in the emergency department compared with those who received placebo (46/71). This difference was statistically significant (RR 1.33; 95% CI 1.10 to 1.62). Fewer children treated with oral ondansetron required IVT (8% estimated from histogram) or were admitted to hospital (2/74) compared with those treated with placebo (22.5% and 11/71, respectively) (RR 0.42; 95% CI 0.17 to 1.00 and RR 0.15; 95% CI 0.03 to 0.71, respectively). The mean number of diarrhoeal episodes while undergoing rehydration (mean length of stay in emergency department 106 minutes ondansetron group versus 120 minutes placebo group) was statistically significantly higher in children who had received ondansetron (mean 1.40) compared with the placebo group (mean 0.50) ($P < 0.001$) even after adjustment for number of episodes prior to admission.

The second US trial¹⁶³ recruited children aged 6 months to 10 years presenting to an emergency department with gastroenteritis (defined as at least one episode of vomiting within the 4 hours preceding triage, at least one episode of diarrhoea and mild to moderate dehydration) ($n = 215$). Those with a body weight less than 8 kg, severe dehydration, an underlying disease that could affect the assessment of dehydration, a history of abdominal surgery or hypersensitivity to ondansetron were excluded. Participants were randomised to treatment with oral ondansetron (dose appropriate for age group) ($n = 108$) or placebo ($n = 107$). The methods of randomisation were adequate and treatments were given by a bedside nurse such that the patient, caregivers and outcome assessors were blinded to allocation. The proportion of patients randomised but lost to follow-up was less than 20%. The power calculation presented estimated that to provide the study with a statistical power of 90% to detect a change from 35% in the placebo group to 15% in the treatment group (in the children who vomited during ORT) (type I error 0.05), 215 children would need to be recruited. The primary outcome was the proportion of children who vomited while receiving ORT and the secondary outcomes were episodes of vomiting during ORT, rate of IV rehydration, rate of hospitalisation and diarrhoeal episodes during follow-up (on days 3 and 7 after randomisation). [EL = 1+]

The two groups were comparable at baseline for sex, age, weight, heart rate, dehydration score, the number of vomiting and diarrhoeal episodes prior to presentation, and serum values. Statistically significantly more children in the ondansetron group (92/107) stopped vomiting in the first few hours after treatment compared with those who received placebo (70/107) (RR 1.31; 95% CI 1.12 to 1.54). Fewer of the children receiving ondansetron required IVT (15/107) than those treated with placebo (33/107), the difference being statistically significant (RR 0.45; 95% CI 0.26 to 0.79). There were no statistically significant differences between groups in the numbers of children admitted to hospital or in episodes of diarrhoea while undergoing rehydration (mean length of stay in emergency department 2 hours ondansetron group versus 3 hours placebo group). However, over the next 48 hours, children receiving ondansetron had statistically

significantly more diarrhoea than those receiving placebo. In the first 24 hour period, the mean number of diarrhoeal episodes in the ondansetron group ($n = 64$) was 4.70 compared with 1.37 in the placebo group ($n = 54$) ($P = 0.002$) and in the second 24 hours was 2.98 episodes ($n = 62$) compared with 0.96 episodes ($n = 51$) ($P = 0.015$).

The third trial from the USA¹⁶⁰ included children aged 1–10 years with acute gastritis or gastroenteritis and mild to moderate dehydration who failed ORT in the emergency department ($n = 106$). Exclusion criteria were receipt of anti-emetics in the 6 hours prior to enrolment, underlying chronic illness, shock state requiring immediate IV fluids, severe (10% or more) dehydration, and known sensitivity to 5HT₃ antagonists. Participants were randomised to treatment with oral ondansetron (dose appropriate for weight) ($n = 51$) or placebo ($n = 55$). The methods of randomisation were adequate and the study was conducted double-blind. With estimated failure rates of 30% in the ondansetron group and 60% in the placebo group to achieve a power of 80% with a significance level of 0.05, 48 participants were required in each group. Outcomes were measured daily for up to 6 days or until symptoms resolved if sooner, and were cessation of vomiting, IV fluid administration, hospitalisation and frequency of diarrhoea. [EL = 1+]

Baseline comparability of the groups was similar except that statistically significantly more children in the ondansetron group were 'moderately' dehydrated. Hence more children were mildly dehydrated in the placebo group but this was not statistically significant. Nine percent of participants did not participate in follow-up telephone interviews and three patients in the ondansetron group were incorrectly diagnosed. The investigators reported that 93% of patients who had received ondansetron had fewer than three episodes of vomiting during a 6 day follow-up, compared with 88% of patients in the placebo group. Insufficient data were available to establish the statistical significance of this difference or of the reported mean number of vomiting episodes between the groups. Fewer of the children receiving ondansetron required IVT (9/48) than those treated with placebo (30/55), the difference being statistically significant (RR 0.34; 95% CI 0.18 to 0.65). There was no statistically significant difference between groups in the numbers of children admitted to hospital. Nineth-three percent of patients who had received placebo had fewer than three episodes of diarrhoea during a 6 day follow-up, compared with 80% in the ondansetron group. Insufficient data were available to establish the statistical significance of this difference or of the reported mean number of diarrhoeal episodes between the groups.

Data on cessation of vomiting was extracted from two trials^{163,164} and pooled in a meta-analysis. The results showed that more children in the ondansetron groups stopped vomiting in the first few hours after treatment (146/181) compared with those who received placebo (116/178). This difference was statistically significant (RR 1.32; 95% CI 1.17 to 1.49) (Figure 8.1).

All three trials^{160,163,164} compared the effects of oral ondansetron with placebo on IV hydration. These findings were pooled in a meta-analysis which showed that fewer of the children receiving ondansetron required IVT than those treated with placebo (79/233), with the difference being statistically significant (RR 0.41; 95% CI 0.28 to 0.59) (Figure 8.2).

The data from the trials^{160,163,164} were pooled for the number of patients admitted to hospital after the emergency department stay. The findings showed that statistically significantly fewer children given ondansetron were admitted to hospital (9/232) compared with those given placebo (23/233) (RR 0.37; 95% CI 0.17 to 0.82) (Figure 8.3).

The fourth US study¹⁶¹ recruited children aged 6 months to 12 years presenting to an emergency department with paediatrician-identified acute gastritis or gastroenteritis (defined as more than three vomits over previous 24 hours) with mild or moderate dehydration who had failed ORT. Those with current chronic medical disease (excluding asthma), with a history of abdominal surgery, requiring chronic medications, with inhaled or other corticosteroid or anti-emetic use in the previous fortnight or with diagnostic findings inconsistent with isolation acute viral gastritis were excluded. The trial had three arms and participants were randomised to a 10 minute infusion with 0.15 mg/kg IV ondansetron ($n = 46$), 1 mg/kg IV dexamethasone ($n = 55$) or a 10 ml bolus of normal saline (placebo) ($n = 44$). The methods of randomisation were adequate and patients and outcome assessors were blinded to treatment allocation. An *a priori* power calculation was done to estimate the sample size required in each group. The main outcomes measured were need for hospitalisation, tolerance of oral hydration and dehydration status at 2 and 4 hours post treatment, and patients were followed up to 72 hours. [EL = 1–]

The study was terminated early and the reported findings were for approximately half the number of expected participants (137/270). The groups were similar at study entry for age, sex, blood glucose, dehydration status and number of vomiting episodes. The trial found that statistically significantly more children who received placebo (9/44) required admission to hospital compared with those who had received IV ondansetron (2/46) (RR 0.21; 95% CI 0.05 to 0.93). Statistically significantly more children who received IV ondansetron tolerated oral rehydration 2 hours after treatment (39/45) than those who received placebo (29/43) (RR 1.28; 95% 1.02 to 1.68). However, results taken at 4 hours post treatment were not statistically significant. Results for mean IV fluids administered and dehydration status were also similar between groups at 2 and 4 hours post treatment. There were no statistically significant differences between IV dexamethasone and placebo groups in hospital admission rates, the numbers of children tolerating oral rehydration, mean IV fluids administered or dehydration status at 2 or 4 hours.

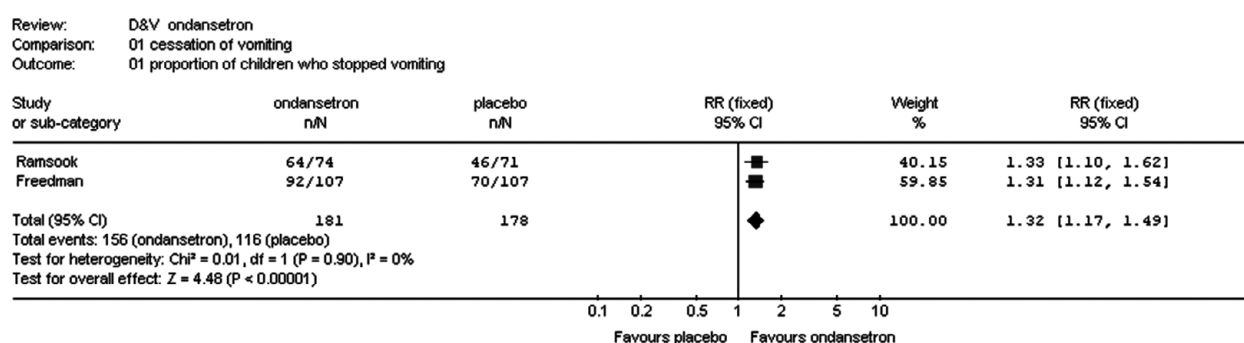


Figure 8.1 Comparison of the effect of ondansetron versus placebo on cessation of vomiting within the first few hours of treatment

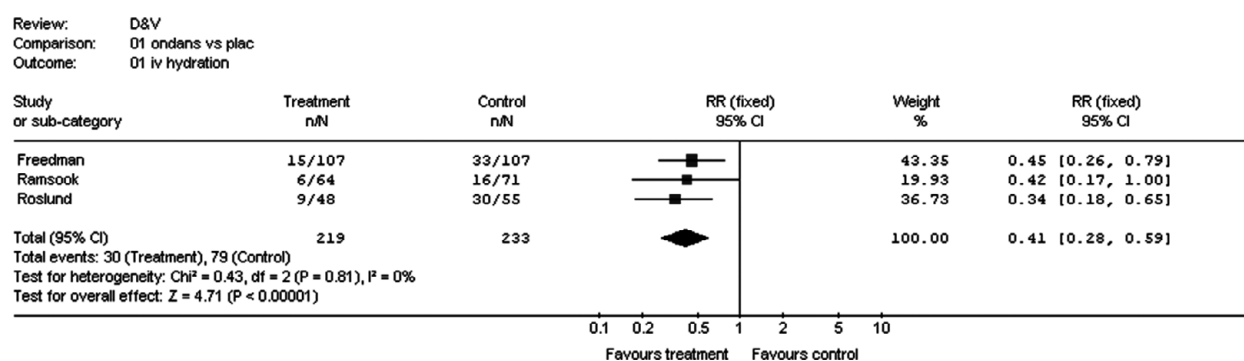


Figure 8.2 Comparison of the effect of ondansetron versus placebo on the need for IVT

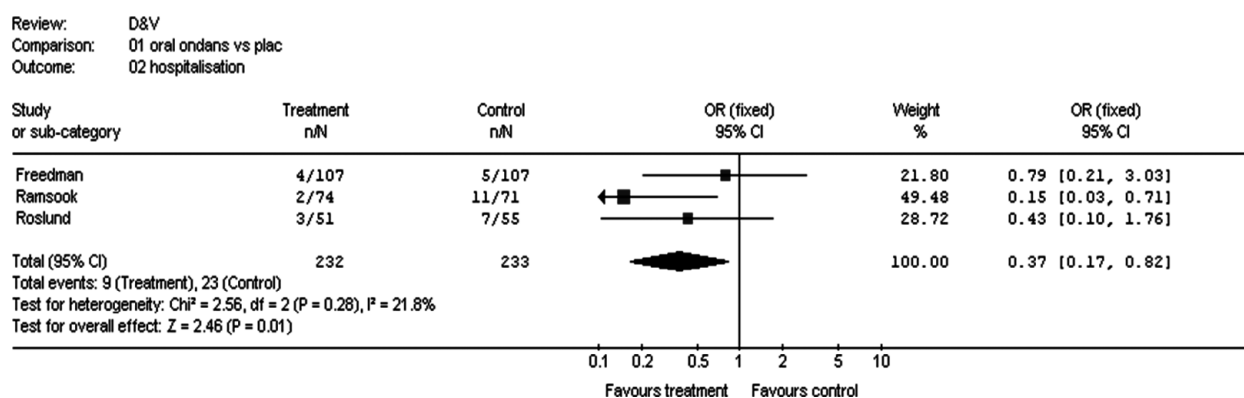


Figure 8.3 Comparison of the effect of ondansetron versus placebo on the need for hospital readmission

The RCT conducted in Venezuela¹⁶⁵ recruited children aged 6 months to 8 years with gastroenteritis with emesis who had vomited twice within 1 hour ($n = 36$). Patients were hospitalised for a minimum of 24 hours. Exclusion criteria were severe dehydration, seizures, rectal temperature of 39 °C or more, parenteral anti-emetic medication in the 6 hours prior to the start of the study or parasite-induced gastroenteritis. The trial had three arms and participants were randomised to a 10 minute infusion with 0.3 mg/kg IV ondansetron ($n = 12$), 0.3 mg/kg IV metoclopramide ($n = 12$) or a 15 ml bolus of normal saline (placebo) ($n = 12$).

The methods of randomisation were not reported although it was stated that pharmacy-controlled medication preparation permitted the patients and outcome assessors to be blind to treatment allocation. The proportion of patients randomised but lost to follow-up was less than 20%. No sample size power calculation was provided.

The groups were different at baseline for age, height, weight and degree of hydration, with comparability on gender and food intake only. There were no statistically significant differences between the IV ondansetron and placebo groups in vomiting or diarrhoea episodes in the first 24 hours. Ten of the 12 children receiving IV metoclopramide had more than four episodes of diarrhoea during the first 24 hours compared with 4/12 children in the placebo group. The difference was statistically significant (RR 2.50; 95% CI 1.08 to 5.79). However, no statistically significant difference was found for emetic episodes between the two groups in the first 24 hours.

Evidence summary

There was evidence from three RCTs [EL = 1+] that supported the effectiveness of oral ondansetron in the treatment of gastroenteritis in children. The meta-analysis performed after extracting the data from two RCTs showed that children with gastroenteritis and receiving oral ondansetron along with rehydration solution were more likely to stop vomiting. Pooled data from three trials demonstrated that the ondansetron group were less likely to require further IVT and less likely to be hospitalised compared with children who had received only rehydration solutions and placebo. No consistent results were found for diarrhoea outcomes. Two of the three trials reported statistically significant results to show that children receiving ondansetron seemed to experience more episodes of diarrhoea.

There was a lack of high-quality evidence for the effectiveness of IV ondansetron, IV metoclopramide and IV dexamethasone in the treatment of children with gastroenteritis. A small RCT [EL = 1–] showed no difference in the cessation of vomiting during the first 24 hours following treatment in children receiving IV ondansetron or IV metoclopramide compared with children treated with placebo. The risk of having more than four diarrhoeal episodes was higher in both the treatment groups (IV ondansetron group and IV metoclopramide group) compared with the placebo group, but the difference was statistically significant only for the IV metoclopramide group.

However, a second underpowered trial did show more children given ondansetron did not require hospitalisation and tolerated ORT more quickly than those given placebo. No statistically significant differences were found between the IV dexamethasone and placebo groups for hospitalisation rates or ORT tolerance.

Cost-effectiveness evidence

A simple economic model was also developed which demonstrates potential economic advantages of ondansetron if given to children with persistent vomiting in whom IV fluids are being considered; further details are provided in Appendix B. Owing to limited evidence for the efficacy of IV ondansetron, the economic analysis only considers the use of oral ondansetron.

The use of anti-emetics such as ondansetron may be effective in the cessation of vomiting and may in turn help with the successful delivery of ORT, thereby reducing the need to treat with IVT. This would have cost-saving implications for the NHS through fewer admissions for IVT. The analysis uses a meta-analysis of three RCTs^{160,163,164} to estimate the difference in effect between placebo and ondansetron for three outcomes: cessation of vomiting, hospitalisation and the need for IVT. Savings in downstream costs were calculated based on the difference in effect obtained with ondansetron. The net cost was calculated by offsetting the cost of ondansetron against the saving achieved with reduced downstream resource use. The analysis suggests that ondansetron,

when compared with placebo, is dominant owing to an increase in the cessation of vomiting and net savings due to a reduction in IVT and lower rates of hospitalisation. A probabilistic sensitivity analysis (PSA) was carried out which showed that the results were not sensitive to parameter uncertainty within the economic model, with ondansetron dominant in 99.96% of simulations. Although some trials reported changes in diarrhoea in response to ondansetron, this was not included in the economic model mainly because of the uncertainty of the clinical significance of this and whether or not increased diarrhoea would lead to increased use of NHS resources. Limitations of the model, particularly with regard to diarrhoeal outcomes, need to be addressed by further research in order to make firm conclusions regarding the cost-effectiveness of ondansetron.

GDG translation from evidence to recommendation

Although many children vomit during ORT, this is usually not so severe as to prevent oral rehydration. Occasionally, vomiting is frequent and persistent. In such cases, a decision might be made to administer ORS solution by nasogastric tube or to change to IVT. The availability of an effective anti-emetic could therefore be very valuable. The GDG considered that evidence from randomised controlled trials indicated that oral ondansetron could increase the success rate with ORT. The GDG was concerned that ondansetron might have adverse effects such as worsening diarrhoea. There was no evidence to support other agents, including metoclopramide and dexamethasone. The GDG concluded that administration of anti-emetics could not currently be recommended. However, the GDG did consider that further research on the use of ondansetron was needed, focusing particularly on the possible risk of worsened diarrhoea.

Research recommendation

In children with persistent vomiting caused by gastroenteritis, is oral ondansetron cost-effective and safe compared with placebo therapy?

Why this is important

Several randomised controlled trials have shown that in children with persistent vomiting during oral rehydration therapy, administration of oral ondansetron, an anti-emetic agent, can increase the likelihood of successful oral rehydration. However, in two of these there was evidence suggesting that diarrhoea was more pronounced in those given ondansetron than in those in the placebo groups. In one, in children given ondansetron, the number of stools passed during the rehydration phase was significantly greater, and in the other the number of stools passed in the first and second 24 hour period after rehydration was significantly greater. In those studies, diarrhoea was not a primary outcome, and it was reported as an adverse event. The reliability of the finding was therefore somewhat uncertain. If ondansetron does worsen diarrhoea it would be crucially important to determine the clinical significance of this effect, for example in relation to the risk of dehydration recurring or re-admission to hospital. If ondansetron is shown to be both effective and safe in secondary care then studies should also be undertaken to evaluate its use in primary care.

8.2 Antidiarrhoeal agents

A range of drugs have been used as antidiarrhoeal agents in patients with gastroenteritis and other disorders. Adsorbent agents such as clay minerals (kaolin or smectite) and charcoal have been employed. Antisecretory drugs such as racecadotril (a peripherally acting enkephalinase inhibitor) reduce intestinal water and electrolyte secretion. Bismuth subsalicylate (BSS) has a number of properties that may be important in reducing diarrhoea, including inhibition of intestinal fluid secretion, suppression of intestinal inflammation and a bactericidal action. Anti-motility agents such as loperamide may reduce diarrhoea by lengthening intestinal transit time and hence absorption.

Nowadays it is generally advised that these medicines should be avoided in the treatment of children with gastroenteritis. Nevertheless, it was considered important to review the available evidence in relation to the use of these agents.

8.2.1 Adsorbent agents

8.2.1.1 Kaolin

Evidence overview

A trial¹⁶⁶ conducted in the Gambia included children with diarrhoea aged between 3 and 18 months ($n = 97$). Those requiring antibiotic therapy or with positive diagnosis for malaria were excluded. Participants were allocated to treatment with kaolin and ORS solution ($n = 45$) or to administration of ORS solution alone ($n = 52$). The method of randomisation was inadequate (birth order allocation) and allocation concealment and follow-up were not reported. Compliance with the doses of kaolin was poor in 33% of the participants. The outcomes considered were duration of diarrhoea and the number of stools per day in both groups. [EL = 1–]

No statistically significant differences were found between the kaolin and the ORS solution groups in the mean duration of diarrhoeal episodes or in the mean number of stools per day.

Evidence summary

There was a lack of high-quality evidence for the effectiveness of kaolin in the treatment of acute diarrhoea in children. A quasi-randomised controlled trial [EL = 1–] showed no differences in the duration of acute diarrhoea or in the number of stools per day between children receiving kaolin with rehydration therapy and children receiving rehydration therapy alone.

8.2.1.2 Activated charcoal

Evidence overview

One RCT was identified that included 39 children aged between 1½ months and 10 years with acute gastroenteritis and severe dehydration ($n = 39$).¹⁶⁷ [EL = 1–] Children with acute gastroenteritis due to *Entamoeba histolytica* were excluded. Participants were allocated to treatment with activated charcoal with oral and IV rehydration solution ($n = 16$) or oral and IV rehydration alone ($n = 23$). The method of randomisation, allocation concealment, follow-up and baseline comparability of the two groups were poorly reported. The outcomes considered were duration of diarrhoea and fluid therapy administered.

The study found that the group receiving the activated charcoal had a statistically significantly shorter mean duration of diarrhoea (mean 2.12 days) than the control group (mean 3.00 days) (WMD -0.88 days; 95% CI -1.50 to -0.26 days). Children in the activated charcoal group required statistically significantly less ORS solution (mean 3.25 packs) than the control group (mean 5.43 packs), (WMD -2.18 packs; 95% CI -3.84 to -0.52 packs). There was no statistically significant difference in the mean IVT (Ringer's lactate solution) required between groups.

Evidence summary

There was some evidence from a poorly reported RCT suggesting that the additional use of activated charcoal in the treatment of children with gastroenteritis shortened the duration of the diarrhoea and reduced the amount of ORT required when compared with the standard rehydration therapy alone. On the other hand, the same trial showed no difference in the amount of IV rehydration therapy required between the children receiving activated charcoal and the children who did not received the adsorbent agent.

8.2.1.3 Smectite

Evidence overview

One relevant systematic review of trials comparing smectite with placebo or no treatment for diarrhoea in children was identified.¹⁶⁸ This well-conducted systematic review included nine RCTs published between 1986 and 2002. Two trials were conducted in France, one in Italy, one in Lithuania, two in Thailand, one in Egypt and one in China. The nine studies included data from 1238 participants: 622 received smectite and 616 received placebo or no additional treatment. Even though it was reported that the doses of smectite were similar across the studies,

the duration of the intervention varied from 2 to 6 days among six studies, and the remaining three did not report such information. Participants were children aged between 1 and 60 months, and were inpatients and/or outpatients. Definitions for the outcome measures and the resolution of diarrhoea were different among the studies. The methodological quality and conduct of the studies were not uniform. An adequate generation of the allocation sequence was reported only for three trials and the allocation concealment was appropriate only in one. Three trials were double-blinded and in only five was an intention-to-treat analysis performed. Data were extracted for the following outcomes: duration of diarrhoea, frequency of stools, vomiting and adverse events. The review also reported the proportion of patients without diarrhoea by days 3 and 5 as well as the proportion of those presenting diarrhoea for more than 7 days. All the trials had better than 80% follow-up. [EL = 1+]

Data from six trials (1076 patients) were pooled in a meta-analysis that showed a statistically significant reduction in the duration of diarrhoea when smectite was administered (WMD -22.7 hours; 95% CI -24.8 to -20.6 hours). Two studies that provided data on the number of stools were pooled. No statistically significant difference was found between the intervention and the control group in the number of stools during the first 24 hours of follow-up. However, children treated with smectite had a statistically significant reduction in the number of stools from the first 24 hour period onwards: at 24 to 48 hours WMD -0.62; 95% CI -1.0 to -0.2), and at 48 to 72 hours WMD -0.58; 95% CI -0.9 to -0.3). The reviewers pooled the data from four trials together, finding that by day 3 the proportion of children treated with smectite and without diarrhoea was statistically significantly higher than the proportion of children that were not treated with smectite and were without diarrhoea (RR 1.64; 95% CI 1.36 to 31.98). When results were pooled using a fixed effects model, statistically significantly more children treated with smectite (122/128) were cured by day 5 compared with those receiving placebo (106/126) (RR 1.24 (95% CI 1.08 to 1.42). However, as significant heterogeneity was observed ($\chi^2 = 8.01$; $P = 0.02$; $I^2 = 75\%$), the reviewers also presented results using a random effects model, where the difference was not statistically significant (RR 1.19; 95% CI 0.93 to 1.53). A funnel plot and regression asymmetry test ($P = 0.23$ and the 95% CI included 0) did not show any publication or other small-sample bias.

One trial showed a reduction in the risk of having diarrhoea for more than 7 days for those children receiving smectite when compared with the control group (RR 0.60; 95% CI 0.42 to 0.85). No statistically significant difference in the number of vomiting episodes between the two groups was found when the results of two studies were combined. One RCT reported the duration of vomiting and showed no statistically significant difference between the two groups. Another trial found no statistically significant differences between the treatment groups for the incidence of vomiting on day 1 and or on day 3 of the intervention. No statistically significant differences in adverse events associated with treatments were identified and three RCTs reported no adverse events associated with short-term treatment with smectite.

Evidence summary

There was evidence from a well-conducted systematic review [EL = 1+] for the effectiveness of smectite in the treatment of children with diarrhoea. The review showed that children receiving smectite had a reduction in the frequency and duration of diarrhoea, experienced a higher resolution of diarrhoea by day 3 and were less likely to have diarrhoea for more than 7 days. On the other hand, the review showed no statistically significant differences between the smectite group and the control group in the number of episodes or duration of vomiting or in the resolution of diarrhoea by day 5. Statistically significant differences in adverse effects between the smectite and control groups were not reported and some trials reported that no adverse events occurred.

8.2.2 Antisecretory agents

Evidence overview

Two randomised placebo-controlled trials of racecadotril^{169,170} and three trials of BSS were identified.¹⁷¹⁻¹⁷³

8.2.2.1 Racecadotril

Two trials compared the effect of racecadotril with placebo.^{169,170} Both trials had two treatment arms and, in total, data from 307 participants (aged 3 months to 4 years) were collected.

One trial ($n = 135$) conducted in Peru¹⁶⁹ examined the effect of racecadotril compared with placebo in boys aged between 3 and 35 months admitted to hospital for dehydration. The included participants had passed watery diarrhoea for 5 days or less, had passed three or more diarrhoeic stools in the 24 hours prior to admission and had passed one diarrhoeic stool within 4–6 hours post admission. Those with blood in the stool, severe dehydration (inability to drink because of drowsiness) or any serious concomitant illness were excluded. Racecadotril (1.5 mg/kg) ($n = 68$) or placebo ($n = 67$) was randomly administered as a powder every 8 hours for 5 days or until diarrhoea stopped if earlier. Oral rehydration was given as needed to all participants. No details were provided about sequence generation, allocation concealment or blinding of assessors. The recorded outcomes included stool output, duration of diarrhoea and overall cure rate measured at 5 days. [EL = 1+]

Both groups were broadly comparable at baseline. Seventeen percent of all participants were lost to follow-up. A statistically significant difference was reported in the mean 48 hour stool output favouring racecadotril over placebo for all participants and for both the rotavirus positive and negative groups. For all 135 participants, the mean stool output in the first 48 hours was 92 ± 12 g/kg in the racecadotril group ($n = 68$) compared with 170 ± 15 g/kg in the placebo group ($n = 67$) ($P < 0.001$). A statistically significant reduction in mean stool output was also observed in the rotavirus-positive participants ($n = 73$). In the racecadotril group ($n = 34$), the mean stool output in the first 48 hours was 105 ± 17 g/kg and 195 ± 20 g/kg in the placebo group ($n = 39$) ($P < 0.001$). The authors stated that in the rotavirus-negative subgroup ($n = 62$) there was a statistically significant reduction in the mean 48 hour stool output in participants receiving racecadotril compared with those receiving placebo (31% lower in the racecadotril group; 95% CI 16% to 46%; $P < 0.001$). For all participants, the mean hourly rate of stool production in first 48 hours was statistically significantly lower in the racecadotril group (1.8 ± 0.2 g/kg/hour) compared with the placebo group (3.1 ± 0.3 g/kg/hour) ($P < 0.001$). The mean total stool output before recovery was statistically significantly lower in the racecadotril group (157 ± 27 g/kg) compared with the placebo group (331 ± 39 g/kg) ($P < 0.001$). This was also observed in the rotavirus-positive participants ($n = 73$): in the racecadotril group ($n = 34$) the mean stool output was 174 ± 36 g/kg and in the placebo group ($n = 39$) it was 397 ± 37 g/kg ($P < 0.001$). Although no further details were provided, the authors stated that in the rotavirus-negative subgroup ($n = 62$), there was a statistically significant reduction in the mean stool output before recovery in participants receiving racecadotril compared with those receiving placebo (37% lower in the racecadotril group; 95% CI 20% to 56%; $P < 0.001$). The median duration of diarrhoea was shorter for the racecadotril group than the placebo group in both the rotavirus subgroups. In both subgroups, the median duration of diarrhoea was 28 hours for the racecadotril group. However, in the placebo group the rotavirus-positive participants had a median duration of diarrhoea of 72 hours compared with 52 hours in the rotavirus-negative participants ($P < 0.001$). In all participants, at 5 days, 57 of the racecadotril group ($n = 68$) were cured of diarrhoea (passing of two consecutive formed stools or not having passed a stool for 12 hours) compared with 44 cured participants in the placebo group ($n = 67$). This difference was statistically significant (RR 1.28; 95% CI 1.04 to 1.56; $P = 0.02$).

A multicentre RCT ($n = 172$),¹⁷⁰ conducted in 13 centres in France, examined the effect of racecadotril compared with placebo in children of both sexes aged between 3 months and 4 years hospitalised for severe acute diarrhoea. Included participants had passed watery diarrhoea (three watery stools per day or more) for less than 72 hours' duration and had passed one watery stool post admission to hospital. Children were excluded if they had chronic diarrhoea, a weight-for-age deficit of 20% or more of the US National Center for Health Statistics (NCHS) standard, a systemic illness or any antibiotic, antidiarrhoeal drug or acetylsalicylic acid usage in the preceding 48 hours. Racecadotril (1.5 mg/kg) ($n = 89$) or placebo ($n = 83$) was randomly administered as a powder three times daily for 5 days or until diarrhoea stopped if earlier. Rehydration was administered orally or by gastric tube without restriction. No details were provided about sequence generation, allocation concealment or blinding of assessors and there were considerable losses in data collection and follow-up (28%). Measures of stool output were presented as both a full data set ($n = 168$) and per-protocol results ($n = 121$). [EL = 1–]

Treatment groups were broadly comparable at baseline. Using the full data set ($n = 167$), the mean hourly rate of stool production in the first 24 hours was statistically significantly lower in the racecadotril group ($n = 85$) (10.5 g/hour) compared with the placebo group ($n = 82$) (16 g/hour) (read from graph). The authors estimated that the treatment difference showed that stool output was approximately 65% of that with placebo (95% CI 44% to 95%; $P = 0.025$). The mean hourly rate of stool production in the first 24 hours was also found to be lower in the racecadotril group ($n = 58$) (11 g/hour) compared with the placebo group ($n = 63$) (17.5 g/hour) in the per-protocol population (read from graph). The authors estimated that the treatment difference showed that stool output was approximately 65% of that with placebo (95% CI 36% to 90%; $P = 0.015$). In the full data set analysis, mean stool output in the first 48 hours was shown to be statistically significantly reduced in the racecadotril group ($n = 84$) (9 g/hour) compared with the placebo group ($n = 82$) (15 g/hour) (read from graph). The authors estimated that the treatment difference showed a 60% reduction in stool output in those receiving racecadotril compared with placebo (95% CI 43% to 88%; $P = 0.009$). Using covariate analysis in the per-protocol population, the mean hourly rate of stool production in the first 48 hours was found to be statistically significantly lower in the racecadotril group ($n = 53$) (8 g/hour) compared with the placebo group ($n = 63$) (16 g/hour) (read from graph). The authors estimated that this indicated a treatment difference of a 50% reduction in stool output (95% CI 33% to 75%; $P = 0.001$). The authors stated that this effect was independent of rotavirus status ($P = 0.5$ for interaction) and that racecadotril was similarly statistically significantly effective in the rotavirus-positive (8 g/hour versus placebo 19 g/hour) and rotavirus-negative (6 g/hour versus placebo 13 g/hour) groups ($P = 0.001$).

Evidence summary

There was evidence from two randomised placebo-controlled trials for the effectiveness of racecadotril in the treatment of diarrhoea in gastroenteritis. One trial conducted in Peru [EL = 1+] and one poorly reported European multicentre trial [EL = 1–] found that children under 4 years given racecadotril (1.5 mg/kg three times daily) and oral rehydration had a reduced total and average hourly stool output 48 hours after starting treatment compared with children given placebo and oral rehydration. The effect on total stool output was independent of rotavirus status. One trial also reported that the rate of stool output was reduced at 24 hours. [EL = 1–] The average stool output before recovery was found to be reduced, irrespective of the child's rotavirus status in one of the trials, which also reported a higher diarrhoeal cure rate at 5 days for children given racecadotril. [EL = 1+] A 'cured' child had passed two consecutive formed stools or no passage of stool for 12 hours.

8.2.2.2 Bismuth subsalicylate

Three RCTs investigating BSS were identified from the searches.^{171–173} One was conducted in Bangladesh,¹⁷¹ one in Chile¹⁷³ and one in Peru.¹⁷² Two trials had two treatment arms^{171,173} and the third had three. Data were collected from 808 children across the three trials although the outcomes considered varied and were as follows: onset of persistent diarrhoea, duration of diarrhoea, intake of oral or IV rehydration and total administration of rehydration solutions, total stool output, total volume of vomitus and duration of hospitalisation.

The largest RCT ($n = 451$)¹⁷¹ compared the effects of administering BSS (100 mg/kg per day) to children presenting with acute diarrhoea with the administration of placebo. The participants were children aged between 4 and 36 months with a history of acute watery diarrhoea. The exclusion criteria were use of antimicrobials within the previous 48 hours, blood in the stool, severe malnutrition, other systemic illness, salicylates intake in the previous 24 hours, allergy to salicylates, or varicella or measles in the previous 3 months. The methods of randomisation and allocation concealment were adequate. Children were followed up for the duration of the hospitalisation and another 4 days. The outcomes measured were onset of persistent diarrhoea, duration of acute diarrhoea (median), total intake of ORS solution and total stool and urine output. [EL = 1+]

The groups were similar at baseline and the loss to follow-up was 8%. The difference in the proportions of children who developed persistent diarrhoea between treatment groups was not statistically significant. The duration of diarrhoea was also found to be similar in children receiving BSS and placebo. However, when considering those children positive to rotavirus, the authors found a statistically significant reduction in the duration of diarrhoea among the children treated

with BSS (median 56 hours) when compared with the children receiving placebo (median 72 hours) ($P = 0.03$). Children treated with BSS had a statistically significant lower output of stool plus urine (mean 386 g/kg, SD 248 g/kg) than the children receiving placebo (mean 438 g/kg, SD 272 g/kg), (WMD -52 g/kg; 95% CI -100 to -4 g/kg). There was no statistically significant difference between the study groups in the mean total intake of ORS solution. While no defined adverse reactions were observed, it was reported that two children had 'black tongue' during treatment.

The second RCT ($n = 142$)¹⁷³ examined the effects of treating children aged between 4 and 36 months and suffering from diarrhoea and dehydration with BSS. The study compared the effects of administering BSS (100 mg/kg) for 5 days ($n = 72$) with placebo ($n = 70$). The exclusion criteria were symptoms that had lasted for more than 72 hours, blood in stools, severe malnutrition, antibiotic use in the previous 48 hours, a salicylate intake greater than 20 mg/kg in the previous 12 hours, allergy to bismuth or to salicylate or acute illness inconsistent with a diarrhoeal state. The method of randomisation was not reported but allocation concealment was adequate. Patients were monitored in hospital for at least 5 days and then were followed for 3 more days (whether they remained in hospital or were discharged). Outcomes measured were disease duration (hours), time to last loose/watery stool, time until last unformed stool, duration of hospital stay and IV fluid intake (ml/kg). [EL = 1+]

The groups were similar at baseline and the loss to follow-up was 13.4%. The use of BSS demonstrated statistically significant benefits compared with placebo in terms of shortening the duration of diarrhoea. The mean time to last loose/watery stool was shorter in the group treated with BSS (mean 73.4 hours) compared with the group receiving placebo (mean 107.5 hours) ($P < 0.02$). The mean time until last unformed stool was also statistically significantly shorter in the group treated with BSS (mean 130.4 hours) compared with the group receiving placebo (mean 170 hours) ($P < 0.01$). The need for IV rehydration therapy was lower in the group treated with BSS than in the placebo group. The difference was reported as statistically significant (data for this outcome have been extracted from a histogram and therefore are estimates). At day 3, the intervention group received on average 30 ml/kg and the control group 45 ml/kg. At day 5, the intervention group intake was on average 20 ml/kg and the control group 42 ml/kg. There was a statistically significant reduction in the duration of hospitalisation among the BSS group compared with the placebo group. The mean of hospital stay for the intervention group was 6.9 days, while for the control group it was 8.5 days ($P = 0.01$). No adverse reactions were observed.

An RCT with three treatment arms ($n = 215$)¹⁷² compared the effects of administering BSS to treat diarrhoea with that of placebo. Participants were boys aged between 6 and 59 months who had acute diarrhoea (three or more watery stools in the preceding 24 hours). The exclusion criteria were presence of blood in the stools, diarrhoea for more than 5 days, use of antibiotics, antidiarrhoeal medication or any treatment with acetylsalicylic acid in the 72 hours before admission, clinical evidence of another illness requiring antibiotic therapy, severe malnutrition, allergy to salicylate or to bismuth or exclusive breastfeeding. The boys were randomised to treatment with BSS 100 mg/kg ($n = 108$), BSS 150 mg/kg ($n = 108$) or placebo ($n = 107$) every 4 hours for 5 days or until the diarrhoea stopped. The methods of randomisation and allocation concealment were adequate. The participants were followed up while in hospital and the outcomes assessed were duration of diarrhoea (proportion of patients with diarrhoea by day 5), total stool output (ml/kg), total volume of vomitus (ml/kg), total intake of rehydration (ml/kg) and duration of hospital stay (days). [EL = 1+]

The groups were similar at baseline and the loss to follow-up was 8% of 275 patients initially enrolled. Diarrhoea stopped within 5 days of admission in 76/85 (89%) children treated with 100 mg/kg BSS, in 73/83 (88%) children treated with 150 mg/kg BSS and in 62/84 (74%) children receiving placebo. By day 5, diarrhoea had ceased in statistically significantly more children in each of the two intervention groups compared with the control group (100 mg/kg BSS RR 1.21; 95% CI 1.05 to 1.40, and 150 mg/kg BSS RR 1.19; 95% CI 1.03 to 1.38). The mean total stool output was 182 ml/kg (SD 197 ml/kg) in children treated with 100 mg/kg BSS ($n = 85$), 174 ml/kg (SD 159 ml/kg) in children treated with 150 mg/kg BSS ($n = 83$) and 260 ml/kg (SD 254 ml/kg) in children receiving placebo ($n = 84$). The mean total stool output was statistically significantly reduced in each of the two intervention groups compared with the control group (100 mg/kg BSS WMD -78 ml/kg; 95% CI -147 to -9 ml/kg, and 150 mg/kg BSS WMD -86 ml/kg; 95% CI -150 to -22 ml/kg). The mean total volume of vomitus was 11.6 ml/kg (SD 19.6 ml/kg) in children treated with 100 mg/kg BSS ($n = 85$), 8.7 ml/kg (SD 18.3 ml/kg) in children treated

with 150 mg/kg BSS ($n = 83$) and 16.2 ml/kg (SD 27.0 ml/kg) in children receiving placebo ($n = 84$). The mean total volume of vomitus was statistically significantly reduced in the group receiving 150 mg/kg BSS compared with the control group (WMD -7.5 ml/kg; 95% CI -14.5 to -0.5 ml/kg). No statistically significant difference in the mean total volume of vomitus was found between the group receiving 100 mg/kg BSS and the placebo group (WMD -4.6 ml/kg; 95% CI -11.7 to 2.5 ml/kg). The mean total intake of rehydration solutions was 239 ml/kg (SD 177 ml/kg) in children treated with 100 mg/kg BSS ($n = 85$), 236 ml/kg (SD 152 ml/kg) in children treated with 150 mg/kg BSS ($n = 83$) and 314 ml/kg (SD 234 ml/kg) in children receiving placebo ($n = 84$). The mean total intake of rehydration solutions was statistically significantly reduced in each of the two intervention groups compared with the control group (100 mg/kg BSS WMD -75 ml/kg; 95% CI -138 to -12 ml/kg, and 150 mg/kg BSS WMD -78 ml/kg; 95% CI -138 to -18 ml/kg). The mean length of hospital stay was 3.3 days (SD 1.5 days) in children treated with 100 mg/kg BSS ($n = 85$), 4.1 days (SD 2.1 days) in children treated with 150 mg/kg BSS ($n = 83$) and 3.4 days (SD 1.5 days) in children receiving placebo ($n = 84$). The mean length of hospital stay was statistically significantly reduced in each of the two intervention groups compared with the control group (100 mg/kg BSS WMD -8.0 days; 95% CI -1.4 to -0.3 days, and 150 mg/kg BSS WMD -0.7 days; 95% CI -1.3 to -0.2 days). The effects of administering BSS 100 mg/kg compared with BSS 150 mg/kg were also reported. No statistically significant differences were observed between the treatment groups for the duration of diarrhoea, total stool output, total volume of vomitus, total intake of rehydration or duration of hospitalisation. No adverse reactions were observed.

Evidence summary

Three RCTs with EL = 1+ were identified for the effectiveness of BSS in the treatment of diarrhoea. Meta-analysis could not be performed because of the variability of the outcomes. Data from two RCTs with small sample sizes showed that children with acute diarrhoea and receiving BSS with ORS solution had a significantly reduced duration of diarrhoea, duration of hospital stay and need for fluid therapy. However, results from the third RCT, which had a large sample size, did not show a statistically significant reduction in the duration of diarrhoea, in the incidence of persistent diarrhoea or in the total intake of ORS solution in the group of children treated with BSS compared with the placebo group. In this trial, a statistically significant reduction in the duration of diarrhoea was seen only for the subgroup of children who were positive for rotavirus. Two trials showed a reduction in the stool output and one trial showed a statistically significant reduction in vomiting in patients receiving a higher dose of BSS. No evidence of benefit was found between the administration per day of 100 mg/kg versus 150 mg/kg of BSS in the treatment of diarrhoea in children for this outcome or any other outcome investigated. No adverse events were identified although two incidents of 'black tongue' during treatment were reported in one trial.

8.2.3 Antimotility agents

Evidence overview

One relevant systematic review of trials comparing loperamide with placebo for diarrhoea in children was identified.¹⁷⁴ [EL = 1+]

8.2.3.1 Loperamide

This well-conducted systematic review¹⁷⁴ included 13 RCTs published between 1980 and 1999. Four of the 13 studies were conducted in European countries, two in South Africa, two in Mexico, one in Costa Rica, one in India, one in Saudi Arabia and two in North Africa (Egypt and Libya). Across the 13 trials, data from 1788 children was collected, 975 were assigned to the intervention group (loperamide) and 813 to the control group. The methodology and conduction of the 13 RCTS was heterogeneous: method of randomisation and allocation concealment were only reported in six and seven studies, respectively, nine trials were double-blinded and two trials did not report inclusion of more than 90% of all randomised participants. Definitions for diarrhoeal resolution, rehydration protocols administered and doses of the study medication varied across the studies. Children recruited in the trials presented with different grades of dehydration and duration of diarrhoea prior to enrolment. However, in most of the trials, participants were mildly

dehydrated and had had diarrhoea for less than 3 days prior to inclusion in the studies). Data were extracted and meta-analysis was performed for the following outcomes: diarrhoea continuing at 24 hours and at 48 hours, reduction in diarrhoea duration, diarrhoea counts for the first 24 hours and adverse events.

In the four trials reporting diarrhoea at 24 hours, the prevalence of diarrhoea among the group treated with loperamide was statistically significantly lower than in the control group (RR 0.66; 95% CI 0.57 to 0.78). When combining the data from the three trials defining the resolution of diarrhoea as the last unformed stool, the findings were not statistically significantly different. Data on the proportion of patients with diarrhoea at 48 hours were available in four studies. The meta-analysis performed showed that the loperamide group had a statistically significantly lower proportion of patients with diarrhoea when compared with the control group (RR 0.59; 95% CI 0.45 to 0.78). The mean duration of diarrhoea was obtained combining the data from six trials. It was found that the group receiving loperamide had a statistically significantly shorter duration of diarrhoea when compared with the control group (WMD -0.80 days; 95% CI -0.87 to -0.74 days). When restricting the analysis to those five studies administering a loperamide dose of up to 0.25 ml/kg per day, the findings were not statistically significantly different. Four studies were included in the meta-analysis for the number of stools at 24 hours. The group treated with loperamide showed a statistically significantly lower mean number of stools than the control group (count ratio = 0.84; 95% CI 0.77 to 0.92). Twelve RCTs reported information on serious adverse events (defined as presence of ileus, lethargy or death). When pooling the data together, it was found that eight participants out of 927 in the intervention group and none out of 764 in the control group underwent some serious adverse event. When abdominal distension and sleepiness were also included among the adverse events, it was found that in total 21 children out of 927 in the intervention group and four out of 764 in the placebo group suffered some kind of adverse event. These last findings were statistically significant.

Evidence summary

There was evidence from a well-conducted systematic review [EL = 1+] for the effectiveness of loperamide in the treatment of diarrhoea in children. Meta-analysis performed in the review showed that children receiving loperamide experienced less stool output and had a reduction of the duration of diarrhoea when compared with children that did not receive the drug. Serious adverse events only occurred in the children receiving loperamide and these participants also had statistically significantly more total adverse events than the children in the control groups.

GDG translation from evidence to recommendation

Diarrhoea is the predominant clinical symptom in gastroenteritis and a major cause of dehydration. It also causes concern to parents who may understandably ask whether there is a treatment available to alleviate it. Various antidiarrhoeal agents have been proposed and some have been widely used. However, as they have been considered relatively ineffective, unnecessary and potentially harmful, their use is avoided.

The GDG considered the evidence available regarding several adsorbent agents (kaolin, charcoal and smectite), an antisecretory agent (racecadotril), BSS and an antimotility agent (loperamide), and drew the following conclusions.

There was no evidence to support the use of kaolin. There was some evidence of possible benefit from activated charcoal but this came from one small study. Young children would probably find this agent unpalatable and adherence would be poor. There was evidence suggesting that smectite was an effective antidiarrhoeal, seemingly without adverse effects, at least in the short term. However, further research would be necessary to examine its potential clinical and health economic benefits in the UK.

There was evidence that racecadotril had an antidiarrhoeal effect but further research is required to examine the possible clinical and health economic benefits that might be associated with its use in the UK.

Studies on BSS had yielded inconsistent results in children and it was thought that any possible benefit was likely to be small.

Clinical trials on the antimotility agent loperamide had demonstrated a statistically significant antidiarrhoeal effect in children with gastroenteritis. Loperamide is not licensed for use in young children with acute diarrhoea in the UK. For that reason, but also given the reported adverse effects such as drowsiness, abdominal distension and ileus, its use was not recommended.

Recommendation on antidiarrhoeal agents

Do not use antidiarrhoeal medications.

Research recommendation

Is racecadotril (an enkephalinase inhibitor) cost-effective and safe in the treatment of gastroenteritis in children compared with a placebo?

8.3 Micronutrients and fibre

Zinc is an important trace element in gastrointestinal structure and function. It is involved in epithelial barrier integrity, tissue repair and immune function. Diarrhoea is associated with significant zinc loss.¹⁷⁵ In developing countries, zinc deficiency may be common owing to inadequate food intake, reduced availability in animal food sources, and high phytate content in the diet resulting in impaired absorption.¹⁷⁶ In 1995, a study from India first reported significant clinical benefit from zinc therapy in gastroenteritis.¹⁷⁷ The WHO has recommended zinc supplementation in children with gastroenteritis. Vitamin A deficiency has been associated with an increased mortality rate in patients with gastroenteritis in developing countries. It has therefore been postulated that supplementation during the acute illness could be of clinical benefit. Glutamine is an amino acid that acts as an important substrate for rapidly dividing cells, including enterocytes and lymphocytes. It has therefore been postulated that glutamine supplementation might be of benefit in gastroenteritis.¹⁷⁸ Folic acid is a water-soluble vitamin with a crucial role in DNA synthesis. It has been proposed that its administration might be beneficial in gastroenteritis, promoting mucosal repair and regeneration and enhancing the immune response.¹⁷⁹ Dietary fibre (soy polysaccharide) supplementation during the illness has been proposed as an effective adjunctive treatment for the reduction of diarrhoea in children with gastroenteritis.

8.3.1 Zinc

Evidence overview

A Cochrane review¹⁸⁰ was identified that included 18 trials in total. Eight of these trials were relevant here^{175,177,181–186} with the remainder being excluded as they had participants who were malnourished or who had persistent diarrhoea.

Three of the studies were conducted in India,^{177,182,185} two in Bangladesh,^{175,184} one in Brazil¹⁸¹ and one in Nepal.¹⁸⁶ The remaining study was a multicentre trial carried out in Pakistan, India and Ethiopia.¹⁸³ Seven studies had two treatment arms and one had three arms.¹⁷⁵ Across the eight studies, 5155 participants suffering from acute diarrhoea (children aged 1–60 months) were enrolled. Four studies were hospital-based trials,^{175,181,182,185} three were community-based trials^{177,177,183} and one study included outpatient participants as well as inpatient.¹⁸⁴

All eight trials included in this review were RCTs. In one study¹⁸⁵ the method used to generate the allocation sequence was unclear but in the other seven trials the method of randomisation was considered adequate. Five studies assured adequate allocation concealment,^{177,182–184,186} but in the remaining three this was unclear.^{175,181,185} The outcome assessor was blinded in seven trials but allocation concealment was unclear in one.¹⁸⁵ Only five trials reported a sample size power calculation.^{175,177,182–184} Seven trials included more than 90% of the randomised participants in the analysis. In one study the number of participants lost to follow-up was unclear.¹⁸⁵ Definition criteria for inclusion of the participants varied between the studies. Dose and duration of the supplementation, formulation and type of zinc salts administered and follow-up were not uniform across all the studies.

Six trials administered zinc alone^{175,181,183–186} and two trials administered zinc with a multivitamin preparation.^{177,182} In one trial¹⁸¹ the placebo group received vitamin C while the intervention group did not. The outcomes measured were duration of diarrhoea, stool output, hospitalisation, adverse events (vomiting) and death. Not all of the studies included reported all the outcomes.

One RCT ($n = 81$)¹⁸¹ was aimed at determining the effect of oral zinc supplementation on the duration of acute diarrhoea in young children. Participants were children aged from 3 to 60 months suffering from diarrhoea for less than 7 days and with, at least, mild dehydration. Children were hospitalised and followed for 5 days or until resolution of diarrhoea. [EL = 1–]

Another RCT ($n = 287$)¹⁸² examined the clinical benefit of zinc supplementation as an adjunct to ORT on stool output and duration of diarrhoea in children with non-cholera diarrhoea. Participants were outpatients aged between 3 and 36 months, with diarrhoea for less than 72 hours and mild dehydration. [EL = 1+] The findings showed that there was no statistically significant difference in the proportion of children with diarrhoea by the 5th day from the start of the study in each of the study groups. The geometric mean of the total stool output in the intervention group was 111 g/kg (95% CI 86 to 147 g/kg) and in the placebo group was 148 g/kg (95% CI 116 to 190 g/kg). The effect size favoured the group receiving the zinc supplementation (ratio of geometric means = 0.69; 95% CI 0.48 to 0.99).

Another RCT ($n = 275$)¹⁷⁵ compared two different doses of zinc supplementation (5 mg and 20 mg of zinc acetate) with placebo on the duration of diarrhoea and stool output in infants with acute diarrhoea. Participants were male infants aged between 1 and 6 months, hospitalised and with diarrhoea for less than 3 days. [EL = 1+] The trial reported the geometric mean and confidence intervals for stool frequency and total stool output. There were no statistically significant differences in either outcome between the groups receiving 5 mg zinc, 20 mg zinc or for those receiving placebo.

A multicentre randomised controlled trial ($n = 1110$)¹⁸³ assessed safety and therapeutic effects of providing zinc supplementation to children suffering from diarrhoea. It compared the impact of administering 10 mg of zinc sulfate per day for 14 days with that of placebo for the treatment of acute diarrhoea. The participants were outpatients aged 1–5 months. [EL = 1+]

Another RCT ($n = 1067$)¹⁸⁴ was aimed at determining whether daily zinc supplementation was associated with an increase risk of vomiting in children with diarrhoea. The study compared 20 mg of zinc supplementation per day for 10 days with placebo. Participants were young children aged between 3 and 59 months with diarrhoea and admitted in hospital or in the outpatient clinic. [EL = 1+]

Another RCT ($n = 50$)¹⁸⁵ assessed the impact of zinc supplementation on the duration of diarrhoea and stool frequency in children with acute dehydrating diarrhoea. It compared the administration of 40 mg of elemental zinc with the administration of placebo in children aged 6–18 months. Participants were hospitalised and followed until recovery. [EL = 1–] It was reported that no vomiting occurred during the follow-up in either group.

Another RCT ($n = 947$)¹⁷⁷ was aimed at evaluating the effects of daily supplementation with 20 mg of elemental zinc on the severity of acute diarrhoea. The study compared the administration of zinc with the administration of placebo. Participants were children aged from 6 to 35 months and who had diarrhoea for less than 7 days. All participants enrolled received multivitamin supplementation. [EL = 1+]

Another study ($n = 899$)¹⁸⁶ was designed to measure the impact of daily zinc supplementation on the duration and severity of acute diarrhoea in children. The trial also assessed the effect of administering zinc with vitamin A but only the zinc-supplemented group and the placebo group have been considered here. Participants were children aged between 6 and 35 months who presented with diarrhoea for less than 96 hours. [EL = 1+] The proportion of children with diarrhoea by the 3rd day of follow-up was reported. It showed a statistically significant difference favouring the group that received the zinc supplementation (27% of children with diarrhoea) when compared with the group receiving the placebo (35% of children with diarrhoea) (RR 0.75; 95% CI 0.61 to 0.91). When the two treatment groups were compared, the ratio of the geometric means of the number of stools in the first 4 days of follow-up showed a statistically significant difference that favoured the group receiving the zinc supplementation (RR 0.91; 95% CI 0.85 to 0.97). Vomiting was found to be significantly higher in the zinc supplementation group (16%)

compared with the placebo group (8.7%) (RR 1.7; 95% CI 1.4 to 2.2), although vomiting events were equal among the two groups.

Five trials reported the mean duration of diarrhoea. The results of these trials are presented according to participants' age (Figure 8.4). One small trial¹⁸¹ reported a statistically significant reduction in the mean duration of diarrhoea for children given zinc compared with those given placebo (WMD -31.2 hours; 95% CI -46.4 to -16.0 hours). Meta-analysis of all five trials using the random effects model found no statistically significant difference in mean duration of diarrhoea between those receiving zinc ($n = 903$) or placebo ($n = 821$) (WMD -4.4 hours; 95% CI -15.9 to 7.2 hours).

Four trials ($n = 3168$) reported the proportion of children with diarrhoea by day 7. Results are presented according to participants' age in Figure 8.5. Two trials^{182,186} reported that statistically significantly fewer children given zinc had diarrhoea by day 7 compared with those given placebo. The first reported this finding in children aged between 6 and 35 months (RR 0.58; 95% CI 0.38 to 0.87) and the second in children aged between 3 and 36 months (RR 0.11; 95% CI 0.01 to 0.88). However, when the results of the four trials were pooled together, there was no statistically significant difference in the proportion of children with diarrhoea by day 7 between those receiving zinc ($n = 1568$) or placebo ($n = 1600$) (RR 0.90; 95% CI 0.64 to 1.27).

Six trials reported outcomes for stool frequency. Four trials ($n = 2135$) reported the mean number of stools per day. Results are presented according to participants' age in Figure 8.6. Two trials^{177,181} reported that children given zinc had statistically significantly lower stool frequency than those given placebo. The first trial made this finding in children aged between 6 and 35 months (WMD -2.00; 95% CI -3.61 to -0.39) and the second in children aged between 3 and 36 months (WMD -5.20; 95% CI -8.52 to -1.88). Pooled results of the four trials found no statistically significant difference in the mean stool frequency between those receiving zinc ($n = 1056$) or placebo ($n = 1079$) (WMD -0.32; 95% CI -0.8 to 0.17). However a statistically significant reduction in stool frequency was seen in children aged over 6 months (two RCTs, WMD -1.90; 95% CI -3.22 to -0.58).

Six trials reported results for vomiting. Four trials ($n = 2475$) reported the proportion of children who vomited. Results are presented according to participants' age in Figure 8.7. One trial¹⁸⁴ reported that statistically significantly more children given zinc had vomited compared with those given placebo. This finding was reported for children seen in inpatients (RR 1.95; 95% CI 1.64 to 2.32) and outpatients (RR 2.53; 95% CI 2.04 to 3.13). The data from all four trials ($n = 2475$) were combined in a meta-analysis that showed a statistically significant increase of vomiting in children receiving zinc supplementations when compared with children receiving placebo (RR 1.63; 95% CI 1.11 to 2.40).

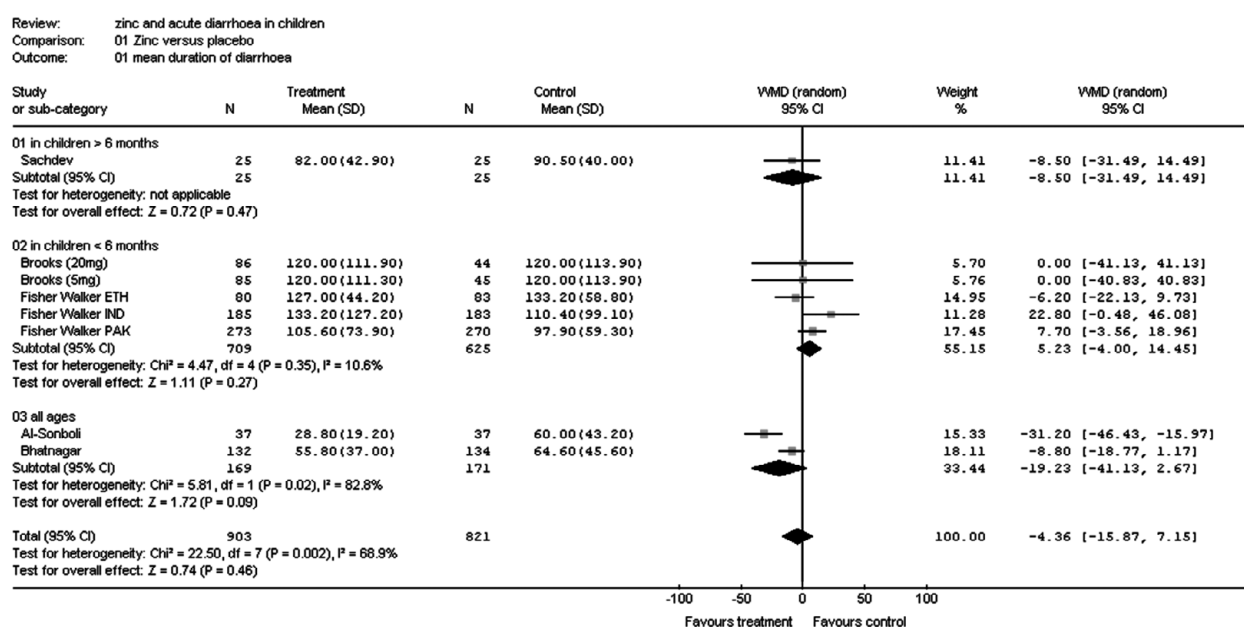


Figure 8.4 Comparison of the effect of zinc versus placebo on the mean duration of diarrhoea

Evidence summary

Eight RCTs, none of them located in European countries, were identified for the effectiveness of zinc supplementation in the treatment of acute diarrhoea in children. Although one small trial demonstrated a statistically significant reduction in duration of diarrhoea in zinc-supplemented children when compared with the control group, results from a meta-analysis (five RCTs) did not find a statistically significant reduction. One study reported that statistically significantly more children who had received zinc did not have diarrhoea at day 3 compared with placebo. Meta-analysis performed regarding the proportion of children with diarrhoea by day 7 (four RCTs) and

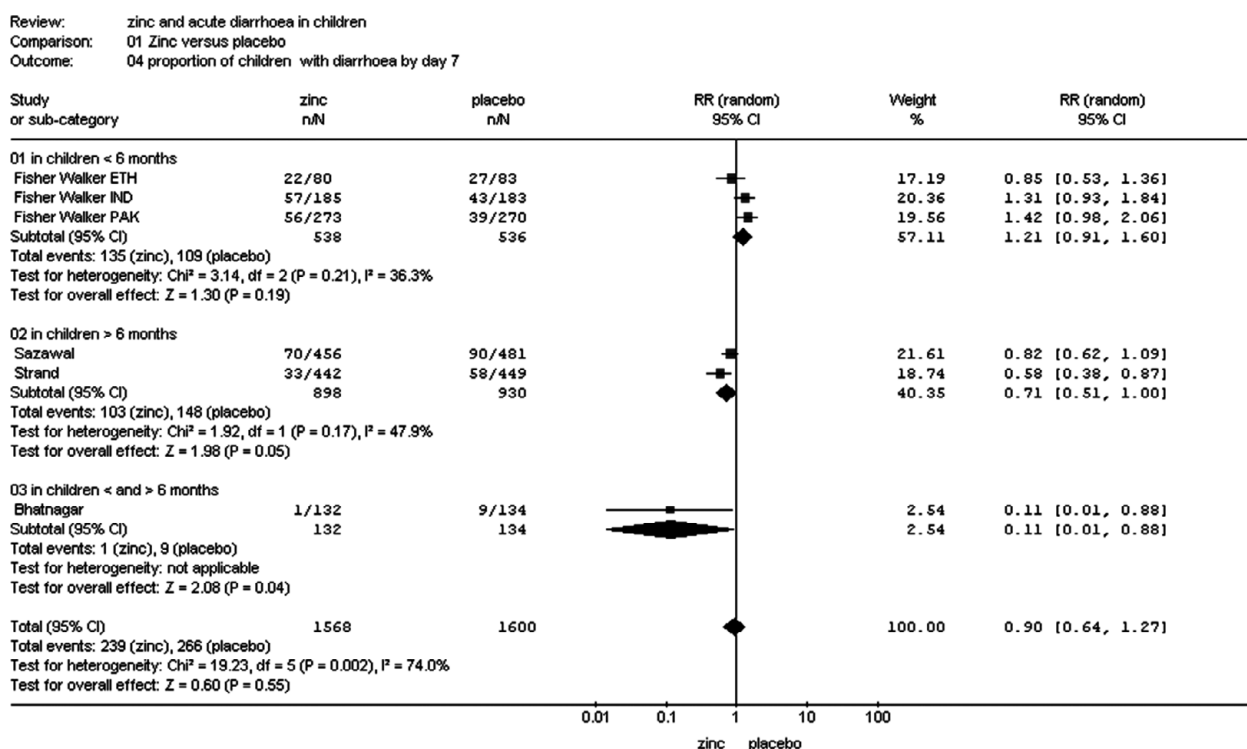


Figure 8.5 Comparison of the effect of zinc versus placebo on the proportion of children with diarrhoea by day 7

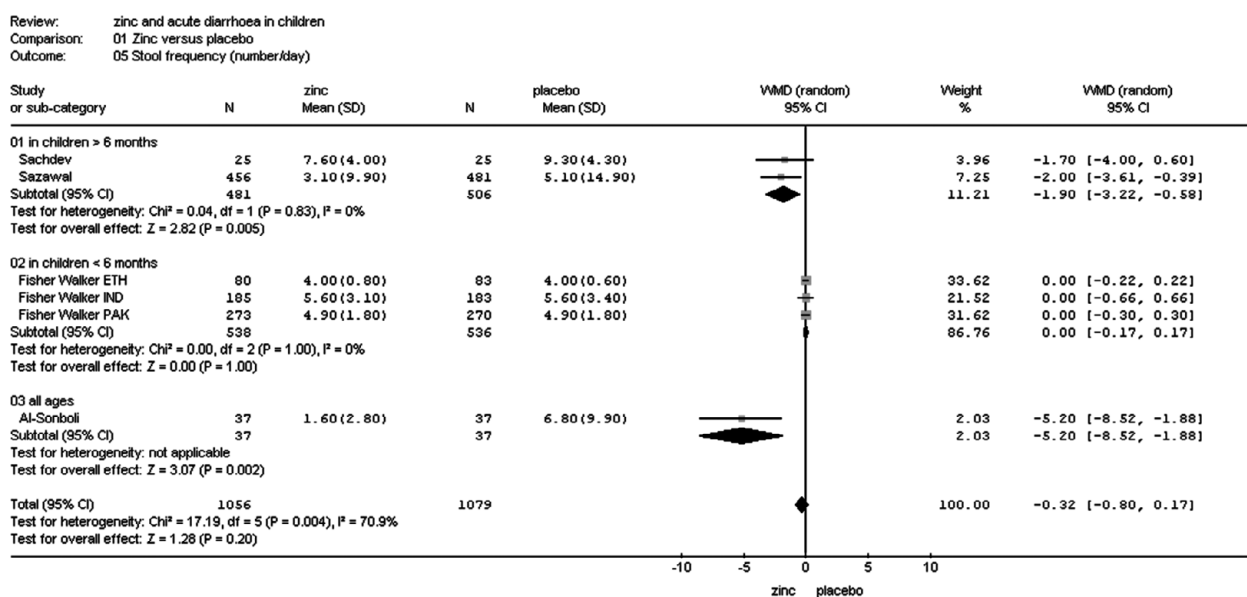


Figure 8.6 Comparison of the effect of zinc versus placebo on stool frequency

stool frequency (four RCTs) showed no statistically significant differences between the zinc and placebo groups, although two studies presenting results for each of these outcomes did report statistically significant improvement with zinc administration. When data from four trials were combined this showed a statistically significantly increased number of vomiting events among children supplemented with zinc when compared with children in the control group. There was significant heterogeneity in the meta-analyses undertaken in this review. Adjustment for nutritional, geographical and treatment differences did not affect the significance of the findings, suggesting that no one single variable explained the heterogeneity found alone. The applicability of these results might therefore be limited to those settings with similar population characteristics.

8.3.2 Vitamin A

Evidence overview

Three trials were identified for this review.^{187–189} Two of these were conducted in Bangladesh^{187,188} and one in Turkey.¹⁸⁹ All three had two treatment arms. In total, data from 286 children (aged 6 months to 7 years) suffering from acute diarrhoea were collected across the three studies. Follow-up, treatment protocol and definition criteria for inclusion of the children with acute diarrhoea varied between the three studies. The outcomes considered were duration of the disease, stool output, vomiting, clinical cure, bacteriological cure and treatment failure.

Two studies compared the effects of 200 000 iu vitamin A with placebo in children with diarrhoea.^{187,188}

One RCT ($n = 83$)¹⁸⁷ examined the therapeutic effect of vitamin A in children suffering from acute diarrhoea. The participants were boys aged between 1 and 5 years presenting with watery non-cholera diarrhoea of less than 48 hours' duration. The study compared the administration of a single oral dose of 200 000 iu vitamin A plus 25 iu vitamin E with the administration of placebo, which consisted on 25 iu vitamin E. The methods of randomisation were adequate. Allocation concealment details were not given, although the patients and outcome assessors were stated to be blinded to treatment allocation. Comparability of the groups at study entry was adequate in all the studies and the proportion of patients randomised but lost to follow-up was under 20%. [EL = 1+]

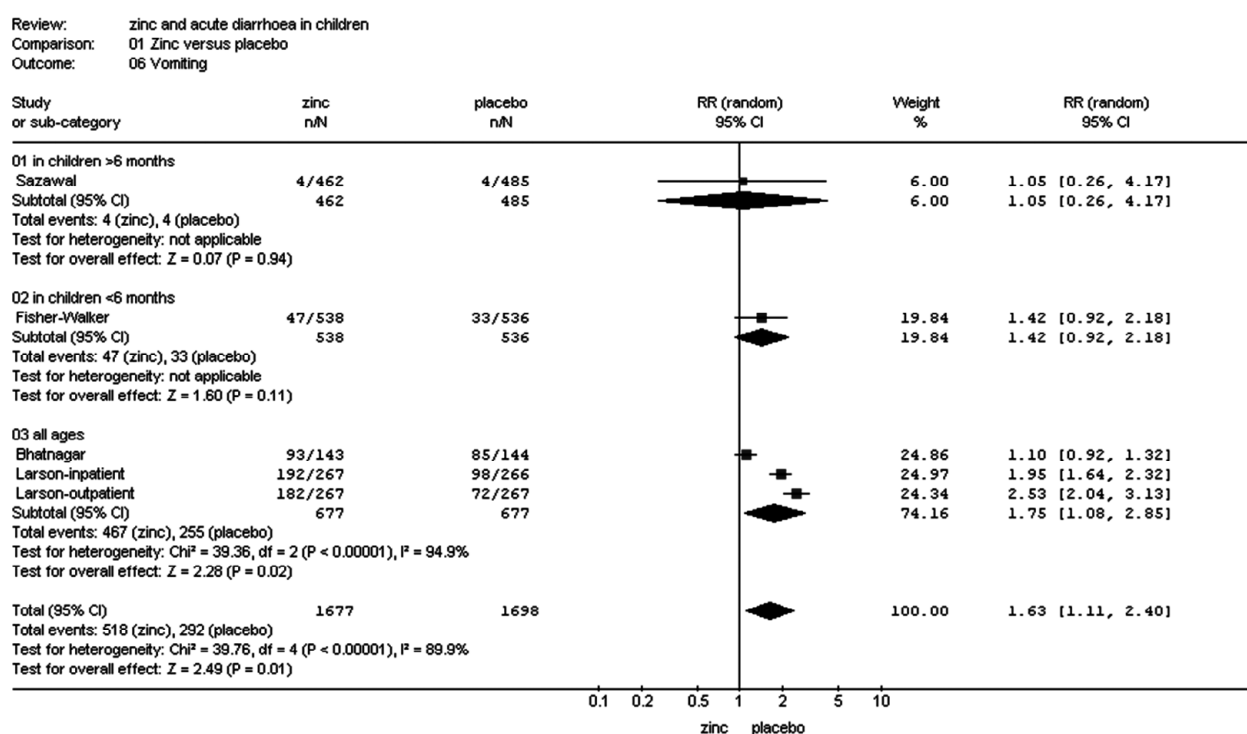


Figure 8.7 Comparison of the effect of zinc versus placebo on the proportion of children who vomited

There were no statistically significant differences between the two groups for the total duration of the diarrhoeal episode, for the proportion of children with a diarrhoeal episode lasting more than 10 days, for the total stool output or for the stool output in the first 24 hours after the start of the intervention. The study found no statistically significant differences between study groups for the volume vomited per day or for the rate of treatment failure (defined by the researchers as the need for IVT after initial oral rehydration).

Another RCT ($n = 90$)¹⁸⁸ examined the effects of a single administration of 200 000 iu vitamin A in children with shigella infection compared with the administration of a placebo. The patients were children aged between 1 and 7 years who had presented to the outpatient department with diarrhoeal stools. The methods of randomisation and allocation concealment were adequate and a sample size power calculation was given. The patients and outcome assessors were blind to treatment allocation. The outcomes measured in the trial were achievement of clinical and bacteriological cure on study day 5. [EL = 1+]

Comparability of the groups at study entry was adequate and the proportion of patients randomised but lost to follow-up was under 20%. 'Clinical cure' was defined as three or fewer formed stools in a day without any visible blood or mucus and absence of fever and abdominal pain. The authors found that 45% of children in the intervention group (19/42) and 20% in the control group (8/41) were clinically cured by day 5. The difference was statistically significant (RR 2.32; 95% CI 1.15 to 4.69). No statistically significant difference in bacteriological cure (defined as the continuous absence of shigella in both stool and rectal swab samples, from study day 3 onwards) was found between the two groups,

A quasi-randomised controlled trial¹⁸⁹ compared the therapeutic value of a single dose of 100 000 iu oral vitamin A in outpatient children with acute diarrhoea against the administration of placebo. The 120 children enrolled in the study were infants aged between 6 and 12 months suffering from acute diarrhoea for less than 5 days. Those with malnutrition, dysentery or a chronic condition were excluded. The method of randomisation was based on the patients' file numbers (odd or even). The patients and outcome assessors were blind to treatment allocation and a sample size power calculation was given. [EL = 1-]

The groups were comparable at study entry. The proportion of patients randomised but lost to follow-up was reported as under 20%. No statistically significant differences in the treatment groups were reported for the mean total duration of diarrhoea or for persistent diarrhoea.

Evidence summary

Two RCTs located in Bangladesh [EL = 1+] and one quasi-RCT from Turkey [EL = 1-] were identified for the effectiveness of vitamin A supplementation in the management of acute diarrhoea in children. Meta-analysis could not be performed because of the variability of the studies. Data from one of the RCTs showed no evidence of benefit in the duration of the diarrhoeal episode, in the stool output, vomiting or number of treatment failures when comparing children that received 200 000 iu of vitamin A with children receiving placebo. The other RCT suggested that children with shigella infection supplemented with 200 000 iu of vitamin A were more likely to have fewer formed stools with absence of fever and abdominal pain by day 5 than the placebo children. The trial did not show a statistically significant difference between the two groups when considering bacteriological cure. The quasi-RCT showed no statistically significant differences in duration of diarrhoea or the onset of persistent diarrhoea between children receiving 100 000 iu of vitamin A and children receiving placebo.

8.3.3 Glutamine

Evidence overview

A single-centre study undertaken in Turkey was identified.¹⁷⁸

The study was a quasi-randomised controlled trial in which a total of 159 infants were enrolled. The participants were children aged 6–24 months with diarrhoea of less than 10 days' duration. Those children with chronic conditions, severe malnutrition, associated infectious diseases or having been under antibiotic or antidiarrhoeal therapy were excluded from the trial. Eligible cases

in the study were divided into two groups according to their hospital file number on admission, and thus allocation concealment was inadequate. The trial assessed the effect of administering 0.3 g/kg per day of glutamine in the treatment of acute diarrhoea in children. Mothers administered the supplement (glutamine or placebo) in three daily doses for 7 days. The authors reported that patients (and carers) and assessors were blinded to the treatment received and the sample size was calculated based on a preliminary study that looked at duration of diarrhoea in 15 subjects. The outcome considered was duration of the diarrhoeal episode. [EL = 1–]

Loss to follow-up was nearly 20%. The comparability between the two groups at the start of the trial was adequate. The mean duration of diarrhoea in the group receiving glutamine ($n = 63$, mean 3.40 days, SD 1.96 days) was shorter than in the control group ($n = 65$, mean 4.57 days, SD 2.48 days). This finding was statistically significant (WMD -1.17 days; 95% CI -1.94 to -0.40 days). Data relating to duration of diarrhoea after treatment were stratified by stool frequency on admission. Children in the glutamine group with a stool frequency below eight per day ($n = 46$) had a mean duration of diarrhoea of 3.30 days (SD 1.96 days) compared with 4.68 days (SD 2.60 days) in those receiving the placebo ($n = 41$). This finding was statistically significant (WMD -1.38 days; 95% CI -2.36 to -0.40 days). When the data collected from the children with high stool frequency, eight or more stools per day, were analysed, no statistically significant difference in mean duration of diarrhoea was observed between the groups. No statistically significant differences in the proportion with persistent diarrhoea or vomiting were found.

Evidence summary

There was a lack of high-quality evidence for the effectiveness of glutamine supplementation in the treatment of acute diarrhoea in children. A quasi-randomised controlled trial conducted in Turkey [EL = 1–] showed no difference in the onset of persistent diarrhoea or vomiting. On the other hand, the study suggested that glutamine supplementation shortens the duration of diarrhoea by 1 day.

8.3.4 Folic acid

Evidence overview

A single study located in Bangladesh was identified as relevant and included in the review.¹⁷⁹ This RCT recruited 106 male children aged between 6 and 23 months who presented with watery diarrhoea (of less than 72 hours' duration) and some degree of dehydration. They were enrolled after admission into the study ward. The participants were randomised into two treatment arms: those receiving 5 mg folate ($n = 54$) and those receiving placebo ($n = 52$) every 8 hours for 5 days. The method of randomisation and allocation concealment were not reported by the authors. Subjects and investigators were blinded to the treatment administered. A power calculation was performed. The outcomes measured were course of illness, stool output, ORS solution intake and IV fluids received. [EL = 1+]

Baseline comparability between the two groups was adequate but loss to follow-up was not reported. No statistically significant differences were observed between the two groups for the mean duration of diarrhoea, the proportion having diarrhoea beyond 5 days, the mean total stool output, the mean total intake of ORS solution or the proportion of all children receiving IVT. Data were also analysed for rotavirus-positive children ($n = 63$) and the results did not show any statistically significant differences in the intake, output or duration of diarrhoea between the folic acid group ($n = 34$) and the placebo group ($n = 29$).

Evidence summary

Evidence from an RCT [EL = 1+] located in Bangladesh suggested that 5 days of folate supplementation for the treatment of children with acute diarrhoea did not reduce the duration of diarrhoea, the stool output, the ORS solution intake or the number of children requiring IVT.

8.3.5 Fibre

Evidence overview

Two RCTs were included in this review.^{190,191} One of the studies was conducted in Peru¹⁹⁰ and the other in the USA.¹⁹¹ Both trials had two treatment arms. In total, they recruited 91 children with acute diarrhoea.

One hospital-based RCT ($n = 34$)¹⁹⁰ examined the therapeutic effect of dietary fibre on the severity and duration of acute watery diarrhoea. The study compared the effects of the administration of a soy protein lactose-free formula with added fibre (0.6 g/ml) with the administration of a soy protein formula without fibre in children. The participants were hospitalised male children aged between 2 and 24 months suffering from acute diarrhoea for less than 96 hours. Although the reported methods of randomisation were adequate, the allocation concealment was unclear. A sample size power calculation was not given. The outcomes considered were duration of diarrhoea (defined as the number of hours post admission until excretion of the last liquid or semi-liquid stool not followed by another abnormal stool within 24 hours) and treatment failure (defined as recurring dehydration above 5%, electrolyte disorders after initial rehydration or important faecal output during intervention). [EL = 1–]

Comparability of the groups at study entry was adequate and the proportion of participants lost to follow-up was 15%. The median duration of diarrhoea after hospitalisation was estimated at 43 hours in the intervention group and 163 hours in the control group. The authors reported the difference as statistically significant ($P < 0.003$). The difference between the two groups for treatment failure was not statistically significant.

One community-based RCT ($n = 55$)¹⁹¹ assessed the efficacy of dietary fibre in reducing the duration of watery diarrhoea in middle-class American children. The trial compared the effects of feeding children aged under 24 months with a soy fibre supplemented infant formula for 10 days against a standard soy formula in shortening the duration of acute diarrhoea. Although the reported methods of randomisation were adequate, the allocation concealment was unclear. A sample size power calculation was not given. The main outcome measured was mean duration of diarrhoea. [EL = 1–]

Comparability of the groups at study entry was adequate and the proportion of participants lost to follow-up was 25%. Results were stratified by age over or under 6 months. When comparing the two study groups in children over 6 months in age, the authors found a statistically significant difference that favoured the administration of formula with added fibre in shortening the duration of the diarrhoeal episode. The mean duration of diarrhoea was 9.7 hours in the intervention group and 23.1 hours in the control group ($P < 0.05$). The difference was not statistically significant when they compared the mean duration of diarrhoea in infants younger than 6 months. The authors reported for all children that there was no statistically significant difference in the duration of diarrhoea between the children formula-fed with added dietary fibre (12.2 hours) and the ones fed with no added fibre (16.9 hours).

Evidence summary

There was a lack of high-quality evidence on the clinical effectiveness of administering soy protein formula with added fibre in children with acute diarrhoea. Data from one RCT located in Peru [EL = 1–] showed a statistically significant reduction in the duration of diarrhoea but no difference in the number of treatment failures between the group receiving the fibre supplementation and the control group. Another RCT conducted in the USA [EL = 1–] suggested that, in children aged over 6 months, supplementation with fibre shortened the duration of diarrhoea by more than 12 hours. However, no statistically significant effect was observed in the combined group (under and over 6 months of age) or in children younger than 6 months.

GDG translation from evidence to recommendation

Many of the studies on the effectiveness of micronutrients and vitamins in the treatment of gastroenteritis were carried out in populations at risk of nutritional deficiency.

The GDG was aware that a recent Cochrane review had concluded that zinc supplementation could be effective in the treatment of diarrhoea and vomiting in children with gastroenteritis in areas where diarrhoea was an important cause of child mortality. The studies judged relevant to this guideline demonstrated some benefit from zinc in reducing stool frequency but not the mean duration of diarrhoea. There was some evidence that zinc treatment is associated with increased vomiting. The GDG therefore concluded that there was insufficient evidence to justify recommending zinc supplementation for well-nourished children with gastroenteritis.

There was no research evidence that vitamin A administration had a beneficial effect in children with gastroenteritis (with the possible exception of those with shigella), despite the fact that most of the trials took place in settings where malnutrition might be expected. There was little evidence to support a beneficial effect from glutamine supplementation in the treatment of gastroenteritis. There was no evidence to support the use of folic acid therapy, with no benefit being seen in a study carried out in a population that might have been at risk of malnutrition. Although there was some evidence suggesting possible benefit from the use of fibre-supplemented milk formulas in reducing the duration of diarrhoea, the trials were not of high quality.

8.4 Alternative and complementary therapies

Evidence regarding the possible value of alternative or complementary therapies in the treatment of gastroenteritis was sought. Only two studies of homeopathy remedies were identified and examined.

Evidence overview

A systematic review and an RCT were identified that examined the effects of homeopathy compared with placebo for the treatment of acute diarrhoea in children.

The systematic review¹⁹² examined the effectiveness of individualised homeopathy therapy (with one of 19 possible prescriptions) compared with placebo for the treatment of acute diarrhoea in children. [EL = 1–] The results of three RCTs were included and meta-analysed in the review. The trials had been conducted by the review's first author in Nicaragua (two RCTs: pilot study ($n = 33$) and main study ($n = 81$)) and Nepal (one RCT: $n = 116$) applying similar methodology and design.

The review included results from 247 children aged 6 months to 5 years with a history of diarrhoea (defined as three or more unformed stools per day) for no more than 7 days (Nicaragua) or 5 days (Nepal). Children were excluded if they had received antidiarrhoeal treatment within 24–48 hours prior to enrolment or if they had severe diarrhoea requiring hospitalisation or IV hydration. Children were assessed on enrolment for baseline characteristics, given ORT as necessary according to WHO recommendations and then interviewed by a homeopathic practitioner who used a computer program to prescribe the appropriate homeopathic treatment from a choice of 19 possible remedies. These had been prepared previously in the USA by a homeopathic pharmacist to a liquid homeopathic dilution in the 30C potency. Randomisation was performed by sequential assignment of children to pre-randomised and coded tubes of either placebo or homeopathic therapy. Parents were instructed to give their child 1 tablet from the prescribed tube after each unformed stool, to be dissolved in the mouth. Follow-up was performed by parents and auxiliary nurses for 5 days (for 6 days in the pilot Nicaraguan trial) after the initial visit. All study staff and the patients were blind to treatment allocation. The primary outcome measures were duration of diarrhoea (defined as the number of days until there were two consecutive days with less than three unformed stools per day) and mean number of stools per day.

When data were pooled, children were similar at baseline for sex and diarrhoeal outcomes prior to study enrolment. However, children in the placebo group were significantly younger, shorter and lighter than those receiving homeopathy treatments. This reflected a discrepancy in randomisation in the Nepali study, as groups were essentially similar at baseline in the Nicaraguan studies. This bias would tend to overestimate any difference in treatment effect seen between the two groups.

Combined results suggested that children receiving homeopathy had a statistically significantly shorter duration of diarrhoea (3.1 ± 2.0 days versus 3.8 ± 1.9 days; $P = 0.008$) and statistically significantly fewer number of stools per day (2.7 ± 2.0 versus 3.4 ± 2.0 stools per day; $P = 0.004$) compared with those receiving placebo. However, as overall children in the placebo group were younger and smaller than those receiving homeopathy, the reliability of the meta-analysis results are questionable.

One RCT¹⁹³ recruited 292 children aged between 5 months and 6 years who presented to a municipal acute care clinic in Honduras. [EL = 1+] The children had acute diarrhoea that was confirmed visually by study staff (defined as the passage of three or more unformed stools in the previous 24 hours). Children were excluded if the diarrhoea had lasted more than 4 days, there was visible blood in the stool, they were severely dehydrated or they lived outside the catchment area of the clinic. Once enrolled, the participants' parents were given bottles of premixed ORT and a vial of tablets. Randomisation was performed by sequential assignment of children to pre-randomised and coded vials of either placebo ($n = 134$) or homeopathic combination therapy ($n = 131$) tablets. The combination therapy was prepared in the USA by a homeopathic pharmacist and contained the five most common single remedies – *Arsenicum album*, *Calcarea carbonica*, chamomilla, podophyllum and sulphur – in a liquid homeopathic dilution in the 30C potency. Parents were instructed to give their child two tablets after each unformed stool, to be dissolved in the mouth, and to give ORT according to WHO recommendations. Follow-up was performed by parents and auxiliary nurses for 7 days after the initial visit or until symptoms resolved, if sooner (defined as two consecutive days with fewer than three unformed stools each day). The main outcome measures were duration of diarrhoea, mean rate of unformed stool passage per day during follow-up and total number of unformed stools during follow-up. All study staff and the patients were blind to treatment allocation.

Results were presented for 265 children (9% loss to follow-up). The groups were similar for age, sex, height, weight, body temperature, vomiting, dehydration status and duration of diarrhoea and unformed stools prior to study entry. There were no statistically significant differences in the distribution of identified pathogens between the treatment and placebo groups. No statistically significant differences between treatment with homeopathic combination therapy or placebo were reported for the three main outcomes of duration of diarrhoea, mean rate of unformed stool passage per day during follow-up or total number of unformed stools during follow-up. Univariate adjustment for baseline characteristics did not alter these results.

Evidence summary

Evidence from a systematic review and meta-analysis of three RCTs suggested that individualised homeopathy treatment reduced the duration and stool frequency of diarrhoea compared with placebo in young children. [EL = 1+] However, as overall the treatment groups were not similar for age, weight and height at baseline, these findings should be treated cautiously as they may overestimate the true treatment effect size.

Evidence from an RCT examining the effects of a combined homeopathy tablet compared with placebo found that there were no differences in effect on duration of diarrhoea, mean rate of unformed stool passage per day during follow-up or total number of unformed stools during follow-up in young children. [EL = 1+]

GDG translation from evidence to recommendation

The GDG considered that the clinical trials assessing homeopathy had significant methodological limitations. Moreover, there was a lack of consistency in the evidence. Therefore, no recommendation was made for the use of homeopathy.

8.5 Probiotics

In 1985, a lactobacillus was identified through screening of bacteria in fermented milk products that was acid and bile resistant, adhered to intestinal epithelial cells.^{140,194} This was *Lactobacillus rhamnosus* GG, a non-pathogenic organism. The current view of probiotic therapy is based on the concept of a normal balanced intestinal microbiota.¹⁹⁵ Much research has been directed towards examining the potential benefit of a variety of probiotics, including various lactobacillus species

and other non-pathogenic microbes in the treatment of infectious gastroenteritis. The possible mechanisms of action include competition with pathogens for binding sites and substrates, lowering of intestinal luminal pH, production of bacteriocins, promotion of mucin production, upregulation of genes mediating immunity, and production of trophic short-chain fatty acids to promote mucosal cell growth and differentiation.¹⁹⁵ The published evidence on the use of probiotics in the treatment of children with gastroenteritis was therefore examined.

Evidence overview

Seven studies were identified for inclusion: three systematic reviews^{196–198} and four RCTs.^{40,199–201}

8.5.1 Lactobacillus and saccharomyces yeast probiotics

One systematic review,¹⁹⁶ published in 2003, was conducted to examine the effectiveness of probiotics compared with control in the treatment of infectious diarrhoea. This well-conducted systematic review included 23 RCTs published between 1981 and 2002. Fourteen studies were carried out in developing countries. The included studies enrolled a total of 1917 participants. Of these, 1449 were children (740 were randomised into the intervention group and 709 into the control group) and 352 were adults (173 were randomised into the intervention group and 179 into the control group). The participants included were inpatients as well as outpatients. Although all the studies enrolled participants with acute diarrhoea, definition criteria were not uniform across the studies. Many studies did not comment on the nutritional status of the participants but those with underlying severe or chronic illnesses were excluded. Two studies recruited specifically malnourished children and a further two studies included malnourished children. The methodology was described in detail and studies were appraised for their quality. The methodology and design of the trials included in the review were not uniform and only three studies reported an adequate method of randomisation, allocation concealment, blinding and loss to follow-up. Different types of probiotic were evaluated and there was a wide range of treatment regimens. The number of organisms administered, duration of treatment, and timing of intervention and means of administration varied across all the studies. Data were extracted and meta-analysis performed for the following outcomes: diarrhoea lasting 3 or more days, diarrhoea lasting 4 or more days, duration of diarrhoea, and mean stool frequency on day 2 and on day 3. Other outcomes reported were need for unscheduled IVT and death. [EL = 1++]

The persistence of diarrhoea on day 3 of the intervention was reported in 15 studies (1341 participants). A meta-analysis was performed that showed that those receiving probiotics were less likely to have diarrhoea lasting 3 or more days (RR 0.66; 95% CI 0.55 to 0.77), but there was heterogeneity ($I^2 = 46.6\%$) between studies. When data from children were pooled (11 RCTs, $n = 1008$), the analysis also showed that statistically significantly more of those receiving placebo (265/490) had persistence of diarrhoea on day 3 compared with those receiving probiotics (195/518) (RR 0.68; 95% CI 0.54 to 0.85; $I^2 = 50.2\%$) (Figure 8.8).

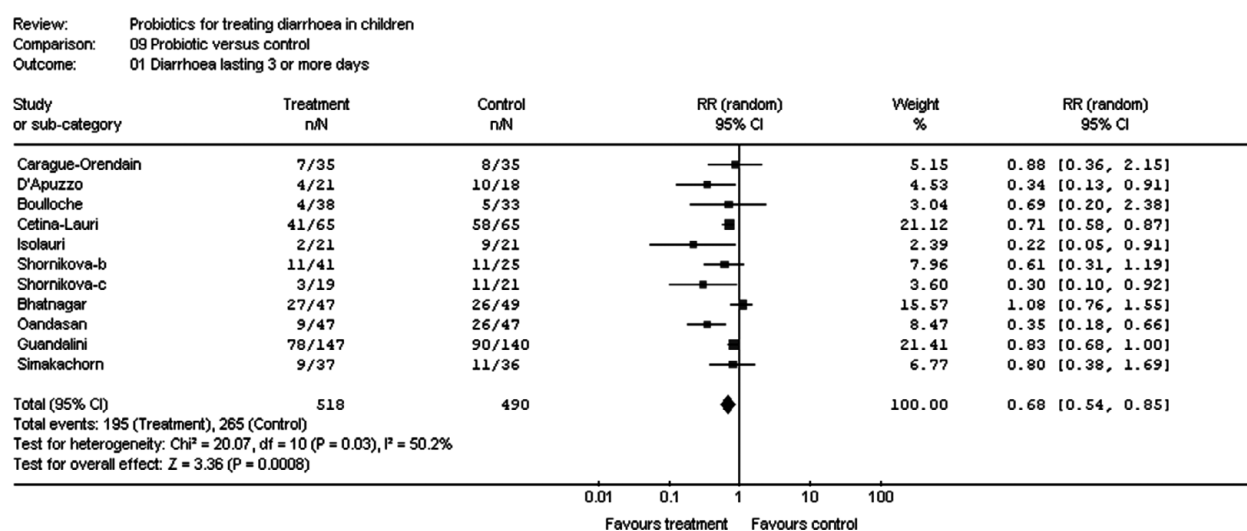


Figure 8.8 Comparison of the effect of probiotics versus placebo on diarrhoea (persistence of diarrhoea on day 3)

Data from 13 studies were pooled in a meta-analysis. The relative risk of diarrhoea lasting 4 or more days in the group treated with probiotics when compared with the control group was 0.31 (95% CI 0.19 to 0.50). However, there was heterogeneity between studies ($I^2 = 72.9\%$). A meta-analysis pooling together the data from the nine RCTs that recruited children ($n = 895$) showed that more of those receiving placebo (168/436) had persistence of diarrhoea on day 4 or beyond compared with those receiving probiotics (79/459) (RR 0.26; 95% CI 0.13 to 0.52; $I^2 = 62\%$) (Figure 8.9).

The mean duration of diarrhoea was measured in 12 studies that included only children. Those children receiving the probiotic agent had a statistically significantly shorter duration of diarrhoea when compared with the children in the control group (WMD -30.5 hours; 95% CI -42.5 to -18.5 hours; random effects model; $I^2 = 85.6\%$) (Figure 8.10).

The mean stool frequency on day 2 was reported in five trials ($n = 417$) and on day 3 it was reported in four trials ($n = 447$). Participants in the probiotic group had statistically significantly fewer stools on day 2 of intervention (WMD -1.51; 95% CI -1.85 to -1.17) and on day 3 of intervention (WMD -1.31; 95% CI -1.56 to -1.07). Data extracted for the stool frequency from the studies that recruited children were included in a meta-analysis. The analysis showed that on day 2 (four RCTs, $n = 232$), children treated with probiotics passed statistically significantly fewer stools than those receiving placebo (WMD -1.01; 95% CI -1.66 to -0.36). On day 3 of intervention (two RCTs, $n = 170$), children in the probiotic group passed statistically significantly fewer stools than children in the control group (WMD -1.12; 95% CI -1.79 to -0.46). The review reported that occasionally children developed severe dehydration requiring parenteral fluid therapy but in none of the studies was this attributable to the administration of the probiotic agent causing an adverse event. No death events were recorded among the included studies.

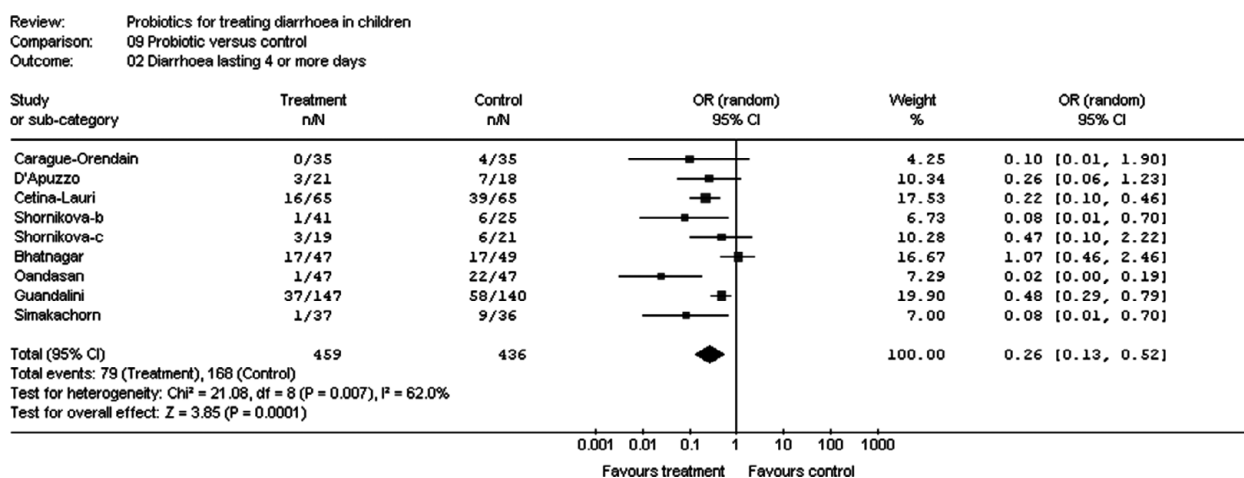


Figure 8.9 Comparison of the effect of probiotics versus placebo on diarrhoea (persistence of diarrhoea on day 4)

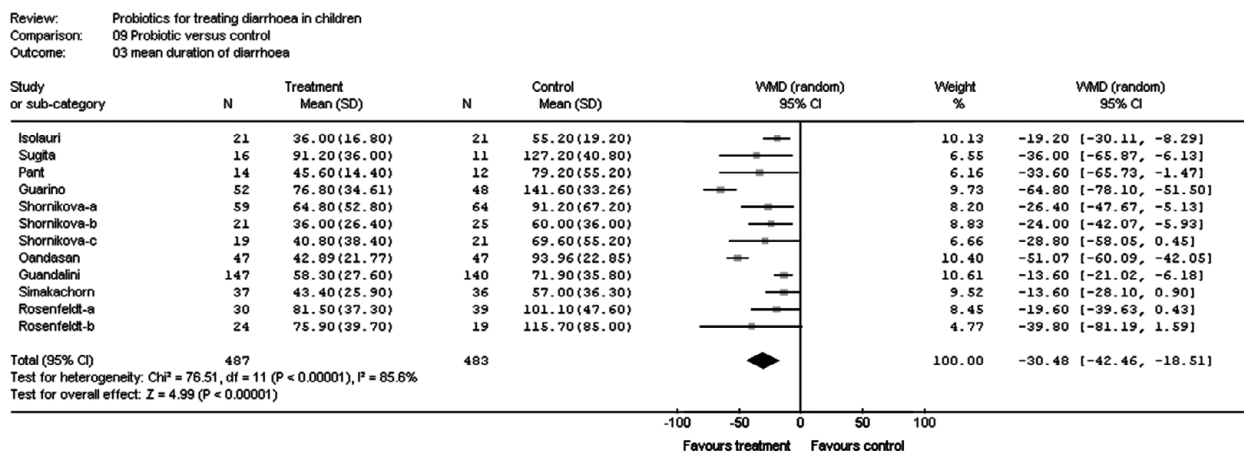


Figure 8.10 Comparison of the effect of probiotics versus placebo on the duration of diarrhoea

Evidence summary

There was evidence from a well-conducted systematic review examining the effectiveness of probiotics compared with control in the treatment of acute diarrhoea in children. The review showed that children receiving a probiotic had a reduction in the duration of diarrhoea and in the stool frequency. However, there was evidence of significant statistical heterogeneity and there was variation across the included studies regarding the specific probiotic employed, the therapeutic regimen used, the methodology and the population included.

8.5.2 *Lactobacillus rhamnosus* GG

One systematic review¹⁹⁷ evaluated the effectiveness of *Lactobacillus rhamnosus* GG in the treatment of acute infectious diarrhoea in children. This well-conducted systematic review included eight RCTs involving 988 participants, 494 in the intervention group and 494 in the control group. Of the eight studies, four were located in European countries, three in South America and one in Pakistan. Participants were children aged between 1 and 36 months with acute diarrhoea, and were inpatients as well as outpatients. They presented with different grades of dehydration and duration of diarrhoea prior to enrolment. However, in most of the trials, participants were mildly dehydrated and had diarrhoea for less than 3 days prior to inclusion in the studies. The trial conducted in Pakistan included undernourished children. Definition criteria for diarrhoeal resolution, rehydration protocols administered and doses of the study medication varied across the studies. The methodology and conduct of the eight RCTs was heterogeneous: method of randomisation and allocation concealment were unclear or inadequate in four and six studies, respectively, two trials were not blinded and three trials did not include an intention-to-treat analysis. In one study, 43% of the participants enrolled did not complete the follow-up. Data were extracted and meta-analysis was performed for the following outcomes: duration of diarrhoea, diarrhoea on day 3, stool output and hospitalisation. In addition, the review looked at vomiting and treatment failure. [EL = 1+]

Seven trials measured the duration of diarrhoea ($n = 876$). The authors of the review performed a meta-analysis (high heterogeneity, with $I^2 = 97.4\%$) showing that children receiving the *Lactobacillus rhamnosus* GG, compared with children in the control group, experienced a statistically significant reduction of 1 day in the duration of the diarrhoeic episode (WMD -1.08 days; 95% CI -1.87 to -0.28 days) (Figure 8.11).

Three trials reported the duration of rotavirus diarrhoea in children ($n = 201$). The data were pooled, despite high heterogeneity ($I^2 = 94\%$), showing that children in the intervention group had a statistically significantly shorter duration of diarrhoea than those children in the control group (WMD -2.08 days; 95% CI -3.55 to -0.60 days). Two RCTs ($n = 303$) showed no statistically significant difference between the children treated with the probiotic and the children in the control group. The results of three studies were combined ($I^2 = 86.4\%$) to show that the mean hospital stay was not statistically significantly different among children receiving the *Lactobacillus rhamnosus* GG and the control group. One trial ($n = 36$) measured the number of emetic episodes on day 1 of the study and on day 2. The trial found no statistically significant difference between the two groups in the frequency of vomiting on day 1. On day 2, the difference

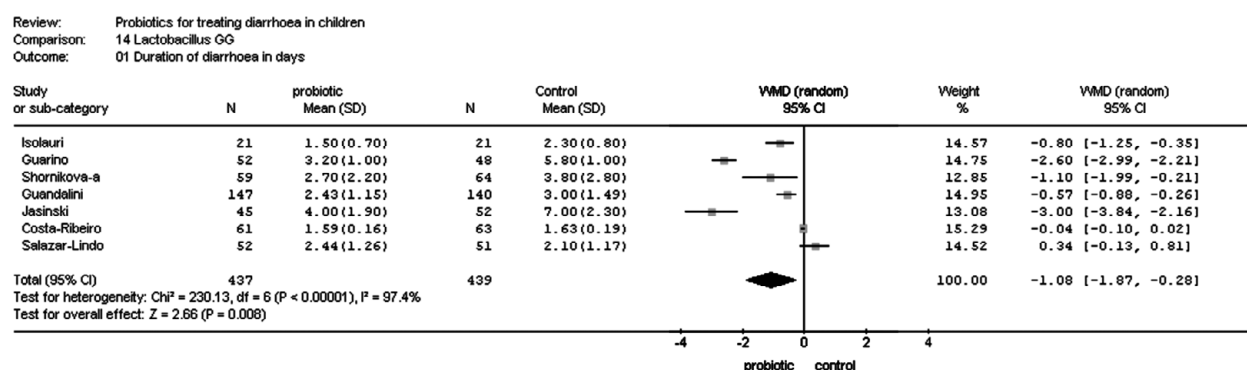


Figure 8.11 Comparison of the effect of *Lactobacillus rhamnosus* GG versus placebo on the duration of diarrhoea

was statistically significant favouring the intervention group (WMD -2.95 ; 95% CI -3.4 to -0.6). One trial reported two cases of myoclonic jerks (one case in each study group) and another trial reported no adverse events.

Evidence summary

There was evidence from a well-conducted systematic review [EL = 1+] for the effectiveness of *Lactobacillus rhamnosus* GG in children suffering from acute diarrhoea. Data from seven trials were combined, showing that children treated with *Lactobacillus rhamnosus* GG experienced a 1 day reduction in the duration of diarrhoea but there was significant statistical heterogeneity. Analysis performed on total stool output and hospitalisation showed no statistically significant difference between children receiving *Lactobacillus rhamnosus* GG and children that did not receive the probiotic.

8.5.3 *Lactobacillus acidophilus* LB

Evidence overview

One RCT was identified for inclusion.²⁰¹ This study, conducted in Peru, randomised a total of 80 children with acute diarrhoea presumed to be of infectious origin into two treatment arms (40 participants in each group). Children with signs of dehydration requiring hospitalisation and those with illnesses other than the acute diarrhoeal episode were excluded. *Lactobacillus acidophilus* LB administration over 4.5 days was compared with placebo. Methods of randomisation and allocation concealment were unclear although the study was stated to be double-blind. [EL = 1+].

The baseline comparability of the two groups at the start of the study was adequate. Three participants out of 80 were lost to follow-up. No statistically significant differences were observed between the two groups for any of the outcomes considered, which were duration of diarrhoea, proportion of children with diarrhoea at the end of the study, total ORS solution intake and vomiting. One child in the probiotic group had severe dehydration and was withdrawn from the study and another child from the placebo group developed an itchy rash.

Evidence summary

An RCT located in Peru [EL = 1+] examined the effectiveness of *Lactobacillus acidophilus* LB in the treatment of acute diarrhoea in children. It showed no statistically significant differences between the probiotic group and the placebo group when considering duration of diarrhoea, ORS solution total intake, vomiting, adverse events and proportion of children without diarrhoea by the end of the study.

8.5.4 *Lactobacillus paracasei* strain ST11

Evidence overview

One RCT conducted in Bangladesh was identified.²⁰⁰ In total, 230 male infants and young children aged 4–24 months in the course of diarrhoea of less than 48 hours' duration were randomly divided into two treatment arms to evaluate the therapeutic benefit of administering lyophilised *Lactobacillus paracasei* strain ST11 ($n = 115$) compared with placebo ($n = 115$) for 5 days. Children with bloody diarrhoea, with severe malnutrition or requiring antibiotic therapy were excluded. Children whose stool sample resulted positive for *Vibrio cholerae* were also excluded. The method of randomisation and allocation concealment were adequate. The trial was performed double-blind. The outcomes measured were mean duration of diarrhoea, cessation of diarrhoea, total stool output and total ORS solution intake. Participants were followed in hospital for 6 days or until cessation of diarrhoea. [EL = 1+]

The baseline comparability of the two groups under study was adequate and the loss to follow-up was 11.8%. There were no statistically significant differences in the findings for the two groups for the mean duration of diarrhoea, the proportion of children without diarrhoea by the end of the 6th day, the mean total stool output and the mean total ORS solution. Findings for children requiring IV fluids were not statistically significantly different overall and for rotavirus-infected ($n = 130$) children. However, when non-rotavirus-infected children were considered ($n = 63$),

the probiotic showed a statistically significant positive effect in reducing the total ORS solution intake and the stool output, and in increasing the number of patients with resolution of diarrhoea by the end of follow-up.

Evidence summary

An RCT conducted in Bangladesh [EL = 1+] evaluated the effectiveness of *Lactobacillus paracasei* strain ST11 in the management of acute diarrhoea in children. The study found no statistically significant differences between children treated with the probiotic and children that received placebo regarding the duration of diarrhoea, the total stool output, the total ORS solution intake, the number of children without diarrhoea by the end of the study or the number of children requiring IV fluids. However, they found the probiotic to have a clinical benefit when considering data from non-rotavirus-infected children only.

8.5.5 *Lactobacillus rhamnosus* strains 573L/1, 573L/2 and 573L/3

Evidence overview

One RCT was identified for inclusion.⁴⁰ This trial, conducted in Poland, randomised a total of 93 children aged between 2 months and 6 years with acute diarrhoea into two treatment arms to assess the effectiveness of administering *Lactobacillus rhamnosus* strains 573L/1, 573L/2 and 573L/3 for 5 days compared with placebo. Patients with chronic diseases, immunosuppressive conditions or exclusively breastfed were excluded. Methods of randomisation and allocation concealment were adequate. Investigators and patients were blinded to the treatment. The outcomes considered were duration of diarrhoea, diarrhoea lasting more than 7 days, IV therapy and adverse events. [EL = 1+]

The baseline comparability of the two groups was adequate and more than 90% of the enrolled participants were included in the study analysis. The study found that the duration of diarrhoea was not statistically significantly different between the treatment ($n = 46$) and placebo ($n = 41$) groups. In rotavirus-infected patients ($n = 39$), children treated with the probiotic had a statistically significant shorter duration of diarrhoea ($n = 22$, mean 77.5 hours, SD 35.4 hours) than children that received placebo ($n = 17$, mean 115.0 hours, SD 66.9 hours) (WMD -37.5 hours; 95% CI -72.6 to -2.4 hours).

The difference in the proportions of cases of diarrhoea lasting more than 7 days in each group was not statistically significant. On admission, children were rehydrated per os or intravenously according to ESPGHAN recommendations. The authors reported that the mean duration of parenteral rehydration required was not statistically significantly different between the two treatment groups. The duration of parenteral rehydration required was statistically significantly shorter among children treated with the probiotic ($n = 22$, mean 14.9 hours, SD 13.7 hours) when compared with children receiving placebo ($n = 17$, mean 37.7 hours, SD 32.9 hours). This difference between the two groups was statistically significant (WMD -22.8 hours; 95% CI -39.5 to -6.2 hours). No adverse events were reported.

Evidence summary

An RCT located in Poland showed no statistically significant differences between the children receiving a probiotic preparation of *Lactobacillus rhamnosus* strains 573L/1, 573L/2 and 573L/3 and the children receiving placebo. When only rotavirus-infected children were considered, the trial showed a statistically significant clinical benefit of the probiotic in reducing the duration of diarrhoea and the duration of the IVT required.

8.5.6 *Saccharomyces boulardii*

One systematic review¹⁹⁸ evaluated the therapeutic effects of *Saccharomyces boulardii* in the treatment of acute diarrhoea in children. The review included five RCTs involving a total of 619 participants. Of these RCTs, two were located in Pakistan, one in Mexico, one in Turkey and one in Argentina. The participants were children aged between 2 months and 12 years suffering from diarrhoea. The systematic review was well conducted. However, all the studies included had methodological limitations: only two trials reported an adequate method of randomisation,

only one had adequate allocation concealment, two were not blinded and three did not apply an intention-to-treat analysis. Meta-analyses were performed for duration of diarrhoea and for number of stools on day 3 and on day 4. Other outcomes measured were resolution of diarrhoea on days 2 and 8, presence of diarrhoea at several time intervals, hospitalisation and vomiting. [EL = 1+]

The meta-analysis performed (four RCTs, $n = 473$) showed that children receiving the probiotic had a statistically significantly shorter duration of the diarrhoeic episode (WMD -1.08 days; 95% CI -1.3 to -0.83 days) (Figure 8.12).

Data from three RCTs ($n = 331$) were combined in a meta-analysis. This showed that children receiving the probiotic had statistically significantly fewer stools on day 3 when compared with the control group (WMD -1.3 ; 95% CI -1.9 to -0.6). The results of two RCTs ($n = 218$) were pooled and also showed a statistically significant reduction in the number of stools on day 4 in those children receiving the probiotic compared with placebo (WMD -1.1 ; 95% CI -1.6 to -0.6). One RCT ($n = 130$) measured the proportion of children without diarrhoea on day 2 and on day 8 from the start of the study. It found that statistically significantly more children in the intervention group experienced cessation of diarrhoea on both study days, when compared with the control group (RR 4; 95% CI 1.8 to 9.1, and RR 1.9; 95% CI 1.4 to 2.8, respectively). The proportion of children with diarrhoea on days 3 and 6 was reported in one study ($n = 101$), which found that the children in the intervention group were more likely to be diarrhoea-free by day 3 and by day 6 when compared with the children in the control group (RR 0.71; 95% CI 0.56 to 0.90, and RR 0.49; 95% CI 0.24 to 0.99, respectively). Another study ($n = 88$) found no statistically significant difference between the two groups for the presence of diarrhoea on day 4. The same study ($n = 88$) measured the proportion of children with diarrhoea on days 6 and 7, as well as the proportion of children with diarrhoea lasting more than a week. It found that the children in the intervention group were statistically significantly more likely to be diarrhoea-free on days 6 and 7 when compared with the control group (RR 0.49; 95% CI 0.24 to 0.99, and RR 0.39; 95% CI 0.20 to 0.75, respectively). In addition, the number of children with diarrhoea lasting more than a week was statistically significantly higher in the control group (RR 0.25; 95% CI 0.08 to 0.83). One RCT ($n = 200$) found that children who were treated with *Saccharomyces boulardii* had a statistically significantly shorter stay in hospital than those children who did not receive the probiotic (WMD -1 day; 95% CI -1.4 to -0.62 days) but that there was no statistically significant difference between the two groups for the duration of vomiting. Adverse events associated with the administration of *Saccharomyces boulardii* were not reported in any of the trials included in the review.

Evidence summary

There was evidence from a well-conducted systematic review [EL = 1+] for the clinical benefit of *Saccharomyces boulardii* in the management of acute diarrhoea in children. Meta-analysis performed showed that the administration of the probiotic shortened the duration of diarrhoea by 1 day and resulted in fewer stools on days 3 and 4, but the authors reported methodological limitations in the included trials.

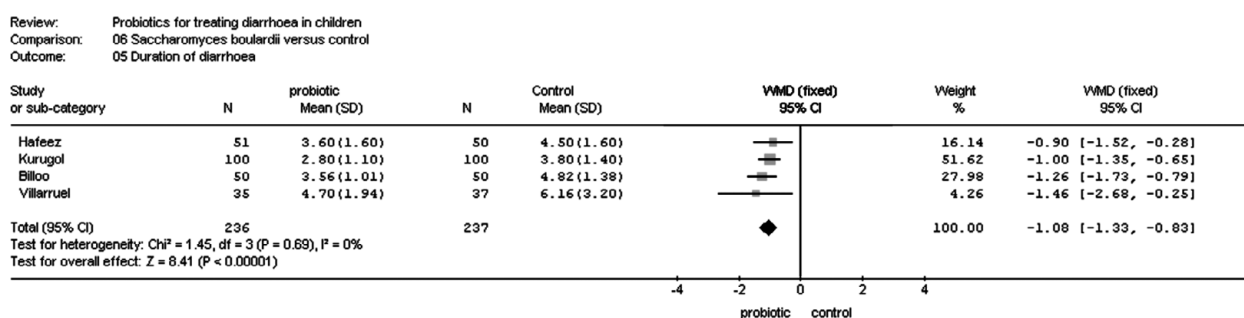


Figure 8.12 Comparison of the effect of *Saccharomyces boulardii* versus placebo on the duration of diarrhoea

8.5.7 *Escherichia coli* Nissle 1917

Evidence overview

One multicentre RCT¹⁹⁹ was identified. The study was carried out in 11 paediatric outpatient centres across Ukraine, Germany and Russia. In total, 113 children aged between 2 and 47 months with non-bloody acute diarrhoea were randomised into two treatment arms (58 patients in the probiotic *E. coli* Nissle 1917 group and 55 in the placebo group) and followed up until treatment response or to a maximum of 10 days. The participants were allocated into the two groups based on random numbers. Allocation was such that participants and outcome assessors were unaware of the treatment given. The authors used an intention-to-treat analysis. The outcomes considered were duration of diarrhoea, proportion of patients without diarrhoea within the 10th day of follow-up and adverse events. [EL = 1+]

The baseline comparability between the two groups at the start of the study was adequate, and 12.3% of participants were lost during follow-up. The treatment response was defined as a reduction in stool frequency to three or fewer watery or loose stools in 24 hours over a period of at least two consecutive days. When comparing the median duration of diarrhoea between the two groups, the authors reported that *E. coli* Nissle 1917 statistically significantly shortened the duration of diarrhoea by 2.3 days (median duration of diarrhoea in the intervention group = 2.5 days, median duration of diarrhoea in the control group = 4.8 days). Diarrhoea stopped within 10 days for 52/55 children in the intervention group and for 39/58 children in the control group. This difference was statistically significant (RR 1.41; 95% CI 1.16 to 1.70). Two children in the intervention group ($n = 55$) suffered from rhinitis and abdominal pain while two children in the control group ($n = 58$) had acute otitis media.

Evidence summary

There was evidence from one multicentre RCT conducted in Russia, Ukraine and Germany for the effectiveness of *E. coli* Nissle 1917 in the treatment of acute diarrhoea in children. The study reported that those children receiving *E. coli* Nissle 1917 probiotic responded to treatment in a statistically significantly shorter time than those receiving placebo. Diarrhoea had stopped by day 10 in statistically significantly more children receiving *E. coli* Nissle 1917 probiotic compared with the placebo.

GDG translation from evidence to recommendation

There were many studies examining the efficacy of probiotic therapy in children with gastroenteritis. There was evidence from a high-quality systematic review suggesting that probiotic treatment had a beneficial effect – shortening the duration of diarrhoea and reducing the stool frequency. However, the available studies varied in quality, in the specific probiotics studied, in the treatment regimens used and in the outcomes examined. Therefore, despite some evidence of possible clinical benefit, the GDG did not consider it appropriate to recommend the use of a probiotic at this time. This was, however, considered to be an important field for further research. Licensed preparations of probiotics are not currently available in the NHS.

Research recommendation

Are probiotics effective and safe compared with a placebo in the treatment of children with gastroenteritis in the UK? Which specific probiotic is most effective and in what specific treatment regimen?

Why this is important

The available studies of probiotic therapy frequently report benefits, particularly in terms of reduced duration of diarrhoea or stool frequency. However, most of the published studies have methodological limitations. Moreover, there is great variation in the specific probiotics evaluated and in the treatment regimens used. Many of these studies were conducted in developing countries where the response to probiotic therapy may differ. Good-quality randomised controlled trials should be conducted in the UK to evaluate the effectiveness and safety of specific probiotics, using clearly defined treatment regimens and outcome measures.

9 Escalation of care

Introduction

NHS Direct is a service that provides telephone-based advice. When a parent or carer calls this service a remote assessment is undertaken. In this context, the term remote indicates that the healthcare professional is geographically remote from the child. Remote assessment is often necessary in other settings and often takes place out-of-hours. When patients request an urgent consultation with their general practitioner, or if they call the ambulance service a remote assessment of the child's needs is necessary.⁵⁶

With remote assessment it is necessary to determine the degree of urgency, the level of care required by the child, and the appropriate care environment. It must reliably identify those children with clinical manifestations suggesting serious illness. However, it is also essential that it successfully identifies those for whom home care is both safe and appropriate.⁵⁶

Healthcare professionals responsible for remote assessment may have varying levels of skill and experience. They can be supported in their role through the use of written protocols or decision-support computer software. Effective remote assessment is a challenge. It must rely completely on the information provided by the caller. Parental anxiety and other factors make the remote assessment of a young child especially challenging. Parents may report the symptom that causes them concern but may fail to reveal other significant manifestations of illness. Close listening and critical thinking are crucial to identifying important cues.⁵⁶

In some circumstances, the healthcare professional may see the child, but physical examination may not be within the scope of practice for that individual. In that circumstance, it may also be appropriate to follow remote assessment guidance.⁵⁶

In all cases, the key escalation of care considerations for the remote assessor are:

1. Is a face-to-face assessment required?
2. Can the child be effectively and safely managed at home?
3. If face-to-face assessment is necessary, should this be in a community or hospital setting?

If there is a face-to-face assessment in a primary care setting and the child can be examined it may be necessary to consider whether referral to a secondary care setting is required.

Clinical question

What key symptoms and signs of gastroenteritis indicate the need for an escalation of level of care?

Evidence overview

Literature searches were performed but no relevant research was identified for inclusion. Therefore, the GDG was assisted in its considerations regarding escalation of care by a Delphi panel consensus employed for the Feverish Illness guideline⁵⁶ on this matter.

That Delphi process identified several factors that should be considered when deciding whether to admit a child with fever to hospital. They were:

- social and family circumstances
- other illnesses that affect the child or other family members
- parental anxiety and instinct (based on their knowledge of their child)
- contacts with other people who have serious infectious diseases
- recent travel abroad to tropical/subtropical areas, or areas with a high risk of endemic infectious disease
- when the parent or carer's concern for their child's current illness has caused them to seek healthcare advice repeatedly

- where the family has experienced a previous serious illness or death due to feverish illness which has increased their anxiety levels
- when a feverish illness has no obvious cause, but the child remains ill longer than expected for a self-limiting illness.

GDG translation from evidence to recommendations

The GDG agreed that there were four considerations that should influence the decision to escalate care:

1. the presence of diagnostic uncertainty
2. the presence of risk factors for dehydration
3. clinical dehydration associated with red flag symptoms and signs (see Table 4.6)
4. other factors:
 - adverse social and family circumstances – the healthcare professional may have concerns regarding the carer's ability to monitor or treat the child appropriately
 - the presence of other illnesses in the child or family members
 - if the carer's concern has led to repeated requests for advice regarding the illness
 - if the parental anxiety and instinct regarding the child's illness (based on their knowledge of their child) is high.

Children in the community might be cared for at home or at an out-of-hours centre with the support of a community children's nursing team, or they might require referral to an emergency department.

In making its recommendations, the GDG considered each of these from the perspectives of healthcare professionals conducting first a remote assessment and second a community-based face-to-face assessment.

Remote assessment

The GDG agreed that children with symptoms or signs suggesting that the child might not have gastroenteritis but an alternative serious condition should be referred for face-to-face assessment in a primary or secondary care setting. The GDG considered that those with risk factors for dehydration, symptoms suggestive of dehydration or adverse social or family circumstances would require a face-to-face assessment. Those with dehydration associated with 'red flags' (see Table 4.6) would usually require assessment in a secondary care setting.

Community face-to-face assessment

Those healthcare professionals responsible for face-to-face assessment in the community should have the necessary knowledge and skills to determine whether referral to secondary care is required. Children with symptoms or signs suggesting an alternative serious condition would require referral to secondary care. Children with dehydration associated with red flag symptoms or signs (see Table 4.6) would either require early and repeated face-to-face review or referral to secondary care, based on professional judgement. Consideration should be given to referring those at high risk of dehydration.

Safety netting

Safety netting is a recognised concept²⁰² taking a number of forms. In the context of gastroenteritis, it might consist of the following: discussion with the parent or carer about the symptoms and signs (especially red flags – see Table 4.6) in dehydration, and shock that they should look for. Written information could also be provided. The parent or carer is then given advice on how and in what circumstances they should seek further advice or request a face-to-face assessment. Where appropriate, it should be agreed that a re-assessment will take place, and the timing and arrangements for that assessment should be made clear.

Good safety netting arrangements ensure continuity of care. They take account of the possibility that the child may deteriorate. The GDG did not consider that it should be prescriptive about precise safety netting arrangements to be employed. These should be determined taking account of local services and professional support.

Recommendations on escalation of care

During remote assessment:

- arrange emergency transfer to secondary care for children with symptoms suggesting shock (see Table 4.6)
- refer for face-to-face assessment children:
 - with symptoms suggesting an alternative serious diagnosis *or*
 - at high risk of dehydration, taking into account recognised risk factors *or*
 - with symptoms suggesting clinical dehydration *or*
 - whose social circumstances make remote assessment unreliable
- provide a 'safety net' for children who do not require referral. The safety net should include information for parents and carers on how to:
 - recognise developing red flag symptoms (see Table 4.6) *and*
 - get immediate help from an appropriate healthcare professional if red flag symptoms develop.

During face-to-face assessment:

- arrange emergency transfer to secondary care for children with symptoms or signs suggesting shock
- consider repeat face-to-face assessment or referral to secondary care for children:
 - with symptoms and signs suggesting an alternative serious diagnosis *or*
 - with red flag symptoms and/or signs of dehydration (see Table 4.6) *or*
 - whose social circumstances require continued involvement of healthcare professionals
- provide a safety net for children who will be managed at home. The safety net should include:
 - information for parents and carers on how to recognise developing red flag symptoms (see Table 4.6) *and*
 - information on how to get immediate help from an appropriate healthcare professional if red flag symptoms develop *and*
 - arrangements for follow-up at a specified time and place, if necessary.

10 Information and advice for parents and carers

Introduction

Parents can be advised that gastroenteritis is common and typically the child recovers quickly and without serious problems. Many children can be safely managed at home under parental supervision. Parents and carers therefore require information and advice on recognising symptoms or signs that should cause concern, on providing appropriate care to prevent or treat dehydration and on maintaining their child's nutritional intake. They need to know specifically who should be contacted if they are concerned. Parents also have key role in the prevention of spread of infection to household members and to the wider community.

10.1 Caring for a child with diarrhoea and vomiting at home

Evidence overview

The recommendations in this chapter are based on evidence that is presented elsewhere in the guideline. The relevant evidence can be found in the following chapters:

- Chapter 3 – Section 3.1
- Chapter 4 – Section 4.1
- Chapter 5 – Sections 5.1, 5.3 and 5.4
- Chapter 6 – Sections 6.1 and 6.2.

GDG translation from evidence to recommendations

The GDG agreed that the following information should be offered to all parents and carers on the management of gastroenteritis.

Recommendations on information and advice for parents and carers

Inform parents and carers that:

- most children with gastroenteritis can be safely managed at home, with advice and support from a healthcare professional if necessary
- the following symptoms may indicate dehydration:
 - appearing to get more unwell
 - changing responsiveness (for example, irritability, lethargy)
 - decreased urine output
 - pale or mottled skin
 - cold extremities
- they should contact a healthcare professional if symptoms of dehydration develop.

Advise parents and carers of children:

- who are not clinically dehydrated and are not at increased risk of dehydration:
 - to continue usual feeds, including breast or other milk feeds
 - to encourage the child to drink plenty of fluids
 - to discourage the drinking of fruit juices and carbonated drinks
- who are not clinically dehydrated but who are at increased risk of dehydration:
 - to continue usual feeds, including breast or other milk feeds
 - to encourage the child to drink plenty of fluids
 - to discourage the drinking of fruit juices and carbonated drinks
 - to offer ORS solution as supplemental fluid
- with clinical dehydration:
 - that rehydration is usually possible with ORS solution
 - to make up the ORS solution according to the instructions on the packaging
 - to give 50 ml/kg ORS solution for rehydration plus maintenance volume over a 4 hour period
 - to give this amount of ORS solution in small amounts, frequently
 - to seek advice if the child refuses to drink the ORS solution or vomits persistently
 - to continue breastfeeding as well as giving the ORS solution
 - not to give other oral fluids unless advised
 - not to give solid foods.

Advise parents and carers that after rehydration:

- the child should be encouraged to drink plenty of their usual fluids, including milk feeds if these were stopped
- they should avoid giving the child fruit juices and carbonated drinks until the diarrhoea has stopped
- they should reintroduce the child's usual diet
- they should give 5 ml/kg ORS solution after each large watery stool if you consider that the child is at increased risk of dehydration.

Advise parents and carers that:

- the usual duration of diarrhoea is 5–7 days and in most children it stops within 2 weeks
- the usual duration of vomiting is 1 or 2 days and in most children it stops within 3 days
- they should seek advice from a specified healthcare professional if the child's symptoms do not resolve within these timeframes.

10.2 Preventing primary spread of diarrhoea and vomiting

Evidence overview

The UK Health Protection Agency and public health physicians are primarily responsible for providing guidance on the control of infection in the home, in childcare, school and healthcare environments.

The GDG was aware of two relevant guidance documents commissioned by the Department of Health^{203,204} addressing the prevention of primary spread in childcare facilities, schools, the workplace and other settings.

GDG translation from evidence to recommendations

Although the intended audiences for these guidelines are healthcare, public health, childcare and educational professionals, the GDG felt that some of the recommendations were also relevant to prevention of primary spread of gastroenteritis in the household. The GDG was aware of the crucial importance of consistent advice for parents and carers in the prevention of spread.

Recommendation on preventing primary spread of diarrhoea and vomiting

Advise parents, carers and children that:*

- washing hands with soap (liquid if possible) in warm running water and careful drying are the most important factors in preventing the spread of gastroenteritis
- hands should be washed after going to the toilet (children) or changing nappies (parents/ carers) and before preparing, serving or eating food
- towels used by infected children should not be shared
- children should not attend any school or other childcare facility while they have diarrhoea or vomiting caused by gastroenteritis
- children should not go back to their school or other childcare facility until at least 48 hours after the last episode of diarrhoea or vomiting
- children should not swim in swimming pools for 2 weeks after the last episode of diarrhoea.

* This recommendation is adapted from the following guidelines commissioned by the Department of Health: Health Protection Agency. *Guidance on Infection Control In Schools and other Child Care Settings*. London: HPA; 2006 [www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358374]
Working Group of the former PHLS Advisory Committee on Gastrointestinal Infections. Preventing person-to-person spread following gastrointestinal infections: guidelines for public health physicians and environmental health officers. *Communicable Disease and Public Health* 2004;7(4):362–84.

Appendix A

Cost-effectiveness of IVT versus ORT for children with dehydration

Introduction

Acute diarrhoea with or without vomiting accounts for approximately 20% of general practitioner consultations and more than 12% of emergency department presentations each year, clearly a substantial proportion of NHS resources. There are wide variations in current practice in both primary and secondary care in the methods of rehydration therapy for treating children presenting with dehydration. The GDG identified a single clinical question comparing the effectiveness and safety of oral rehydration therapy (ORT) against intravenous fluid therapy (IVT) in children with dehydration. The GDG thought that economic considerations would be particularly important in formulating recommendations for this question.

Literature review

A systematic search for published economic evidence was undertaken for this question. The initial search identified approximately 21 articles. An initial screen was used to exclude papers that were clearly not relevant to the research question being addressed and from this six papers were retrieved for further examination. In selecting studies for the review, the main exclusion criteria were as follows:

- primary studies set in developing or low-income countries
- papers in a language other than English
- papers published before 1990
- abstracts
- evidence not related specifically to the clinical or cost-effectiveness of ORT or IVT.

From the six retrieved papers, only one²⁰⁵ was identified as an economic evaluation.

This study aimed to compare nasogastric and IV methods of rehydration for children with acute dehydration in a US setting for children aged between 3 and 36 months presenting with acute dehydration caused by vomiting and/or diarrhoea. Before the study began, all children attempted an oral fluid challenge (OFC). Those unable to tolerate oral fluids as a means of resolving their dehydration were enrolled into the study. The children were then randomly assigned to receive either rapid intravenous hydration (RIV) or rapid nasogastric hydration (RNG) over a period of 3 hours within the emergency department. Patients were also given an OFC before being allowed to be discharged from hospital.

The study reported average per-patient costs for both treatments that included laboratory, supply and staff costs. The cost analysis aimed to measure any saving as a result of using RNG over RIV. The authors did not report any significant complications for RNG; RIV was reported to be complicated by repeated catheter insertions that the authors felt resulted in greater inconvenience, pain and an increased overall cost of care.

No statistical difference in outcomes was found between the two treatment options and the authors therefore conclude that RNG was more cost-effective than RIV, on cost alone. Furthermore, the authors noted that both RIV and RNG were cost-effective alternatives to standard treatment (IVT). The authors also concluded that RNG has fewer associated complications in comparison with RIV.

This study could not be used alone as a basis to guide recommendations on IVT and ORT. It focused on nasogastric methods of rehydration (as a subset of ORT) and rapid IVT, whereas the

clinical question for this guideline sought to compare the cost-effectiveness of ORT, more broadly defined, versus standard IVT. Owing to the lack of relevant published economic evidence, it was decided that a decision-analytic model should be developed for this guideline to compare the cost-effectiveness of ORT versus standard IVT in order to inform GDG recommendations.

Method

A decision-analytic model has been developed in Microsoft Excel® in order to compare the cost-effectiveness of IVT and ORT in the treatment of children presenting with dehydration and vomiting due to gastroenteritis. The structure of the decision tree is illustrated in Figure A.1. The economic model focuses on a cohort of 1000 hypothetical patients presenting in the emergency department with dehydration caused by diarrhoea and vomiting.

The decision tree depicts the various pathways it is assumed a child may follow during treatment of either IVT or ORT. In decision trees, 'time flows from left to right' and branches indicate all feasible pathways and these pathways are contingent on certain events. Such events are defined by nodes, of which there are three types:

- Decision nodes (squares) are used to represent choices for the decision maker, in this case the choice to give IVT or ORT.
- Chance nodes (circles) depict uncertain events within a patient pathway. Each branch at a chance node has a probability attached to it and the probabilities of all branches emanating from a chance node sum to 100%.
- Terminal nodes (arrows) denote the end of the treatment pathway and are assigned a 'payoff', which is the estimated cost to the NHS of a particular patient pathway. In this particular decision-analytic model, the payoff also implicitly assumes patient rehydration.

Model parameters and assumptions

Probabilities

The model probabilities are taken from a Cochrane review⁸³ that reported on the evidence on rehydration and complication rates for ORT and IVT in children up to 18 years of age (Table A.1).

All the studies in the meta-analysis reported on the primary outcome of failure to rehydrate with ORT, although definitions of treatment 'failure' were not identical across the included studies. For the purposes of this analysis, the model assumes that ORT treatment 'failure' is that where IVT would have to be used. Theoretically, IVT should be able to replace fluid lost and manage continuing losses and therefore, for the purposes of this model, we have also assumed that IVT treatment 'failure' is where IVT is required for a longer period of time and this is referred to as

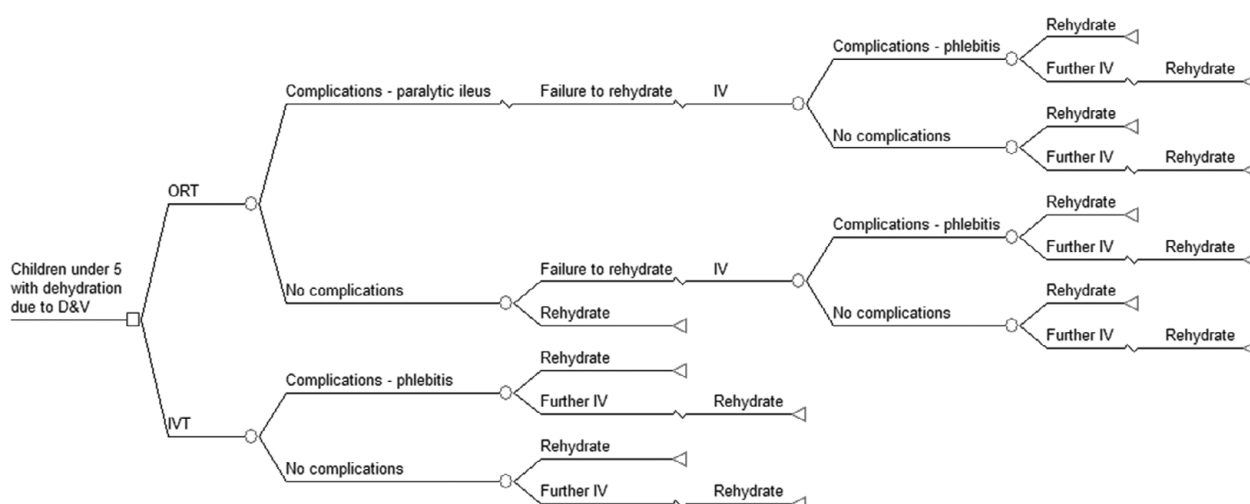


Figure A.1 Decision tree for comparing ORT versus IVT

Table A.1 Meta-analysis of rehydration and complication rates for ORT and IVT; data from Hartling *et al.*⁸³

Outcome	Rate	
	ORT	IVT
Failure to rehydrate ^a	0.065	0.029
Hyponatremia	0.113	0.079
Hypernatremia	0.002	0.002
Paralytic ileus ^a	0.027	0.000
Phlebitis	0.000	0.027
Peri-orbital oedema	0.026	0.026
Abdominal distension	0.017	0.000
Seizures	0.000	0.000

^a Indicates statistical significance at the 5% level.

'further IV'. The model assumes that all patients eventually rehydrate on IVT and therefore all terminal nodes assume rehydration. This assumption essentially means that the two treatments do not differ in their effectiveness and under such a scenario a cost-minimisation analysis may be deemed appropriate. The implications of this will be addressed through a threshold sensitivity analysis and in the discussion.

The decision analysis included only those complications reported in the Cochrane review where there was a difference between the two treatments that was statistically significant at the 5% level. As a result, the only complications modelled were phlebitis and paralytic ileus. It is important to note, however, that statistical significance was not the sole justification for excluding other reported complications. Of the five excluded non-significant complications reported in the meta-analysis, three of them had no difference in mean rates (hypernatremia, peri-orbital oedema and seizures). For hyponatremia although there was a difference in mean rates, the data using a random effects model was highly consistent with a null hypothesis of no difference (95% CI -0.13 to 0.15; $P = 0.9$). The meta-analysis may not have been powered to detect a difference but given the sample size of the meta-analysis this suggests that any 'real' difference that may exist is likely to be very small. It is most unlikely that research would be commissioned that would be powered to detect this and decision makers are likely to have to live with this uncertainty in the foreseeable future. Finally, it was thought that abdominal distension, although more borderline in terms of statistical significance, was probably not of clinical significance.

Table A.2 lists the probabilities used in the analysis. The second column in the table shows the probability values used in the base case analysis. In addition to the base case, a 'worst case' analysis for ORT relative to IVT was also undertaken.* Column 3 gives the range of probabilities used in both analyses.

The Cochrane review also compared ORT and IVT outcomes in terms of weight gain at discharge and duration of diarrhoea. The differences between the two treatments for these outcomes were not statistically significant at the 5% level and therefore these were not incorporated within the economic model.

The review also found that ORT resulted in a statistically significant reduction in length of hospital stay. This was not explicitly included in the model because the costing undertaken as part of this analysis took into account the different resource implications, in terms of hospital stay, of the two treatment options.

Costs

There is variation in how ORT and IVT are delivered, particularly with respect to staff input. In the base case analysis, the aim was to cost up a 'standard' or 'typical' treatment for both ORT

* Derivations of the values used in the 'worst case' analysis are explained later in this appendix.

Table A.2 Probabilities used in the analysis

Item	Value	Range	Source
Failure to rehydrate on ORT with paralytic ileus	1.00	N/A	GDG
Failure to rehydrate on ORT with no paralytic ileus ^a	0.039	0.039–0.042	Hartling <i>et al.</i> ⁸³
Failure to rehydrate on IVT	0.029	0–0.029	Hartling <i>et al.</i> ⁸³
Phlebitis with IVT	0.027	0–0.029	Hartling <i>et al.</i> ⁸³
Paralytic ileus with ORT	0.027	0.027–0.04	Hartling <i>et al.</i> ⁸³

^a The Cochrane review reported that 0.065 patients fail to rehydrate on ORT. However, this review also reported that 0.027 patients with ORT have a paralytic ileus, which we assume always leads to ORT treatment failure. Therefore, we have derived the probability of treatment failure in children with no paralytic ileus as follows:

Probability of ORT failure: 0.065

Probability of no paralytic ileus: $1 - 0.027 = 0.973$

Probability of ORT failure given paralytic ileus: 1.000

The overall probability of ORT failure is a weighted average of ORT failure in children with and without paralytic ileus:

Let y = the probability of treatment failure in those without paralytic ileus

$(0.973y) + (0.027 \times 1.000) = 0.065$

$y = 0.039$

The same method was carried out to derive the upper value of the range.

and IVT as advised by expert opinion within the GDG. Actual costs will vary in different settings and this can be addressed using sensitivity analysis. A ‘worst case’ sensitivity analysis for ORT relative to IVT was also undertaken.

The costing method utilised an ‘ingredients’ or bottom-up approach. This involved detailing the actual resources used in providing treatment (i.e. staffing, consumables, and, where there were differences between treatments, equipment, capital or facilities), obtaining the unit costs of each resource item and multiplying by the quantity of resource used to obtain an estimate of total cost.

Unit costs for staff were obtained from *Unit Costs of Health and Social Care* (2007).²⁰⁶ This publication documents unit costs for a range of professional staff working within the health and social care sector. The costing of staff time includes qualification, training and direct overhead costs in addition to salary/wages and salary oncosts.

Consumable costs relate to resources that are used up in the provision of treatment. Such resource items cannot be reused. Medical equipment was costed by annuitising the initial capital outlay spent on the purchase of equipment over its expected lifespan to give an equivalent annual cost. The formula for calculating the equivalent annual cost is as follows:

$$E = \frac{K - \left[\frac{S}{(1+r)^n} \right]}{A(n,r)}$$

where

E = equivalent annual cost

K = purchase price of equipment

S = resale value

r = discount rate (interest rate)

n = equipment lifespan

$A(n,r)$ = annuity factor* (n years at interest rate)

This equivalent annual cost can then be divided to obtain an estimate of the daily cost of using a piece of equipment.

Finally, there are resources associated with using hospital facilities over and above those that directly relate to rehydration therapy. For example, the ‘hotel costs’ associated with an inpatient admission.

* The annuity factor converts the present value of the equipment into an annuity, which is a series of equal annual payments. This is then divided by 365 to give an equivalent daily cost.

ORT costing

The patient population is defined by attendance at the emergency department. There are opportunity costs associated with an emergency department attendance (administration, cleaning, bed changing, etc.) over and above those relating directly to treatment. However, these opportunity costs do not vary by treatment method and therefore capital costs associated with the use of emergency department facilities can be excluded from the analysis.

ORT costs therefore include only staff and consumable costs. This is due to the omission of emergency department related costs and because patients are discharged following treatment in the emergency department.

Patients undergo a clinical examination prior to receiving ORT; this is done by a specialty registrar.

Patients are then reviewed hourly for the 4 hours they spend in the emergency department; this takes approximately 5 minutes per hour (total of 20 minutes) and is done by a nurse (band 5). Patients also receive education/information regarding the treatment they are being given, also done by a nurse (band 5). This takes approximately 10 minutes.

Table A.3 shows the time taken to carry out ORT-related tasks and the associated costs. Column 2 displays the times used in the base case analysis. The range of times and costs used for both base case and 'worst case' analyses is given in brackets.

Each patient receives an average of two sachets of Dioralyte for ORT, which is given using a 200 ml bottle. Table A.4 summarises the costs for these consumables.

No equipment is required for ORT treatment. It is assumed that all children are discharged from the emergency department once they have received ORT.

IVT costing

As above for the ORT costing, emergency department attendance costs are omitted from the costing of IVT. All children on IVT are given approximately 500 ml of sodium chloride 0.9% saline.*

Table A.5 shows the range of time taken to carry out IVT-related tasks and associated costs. Baseline observations, equipment adjustments and site checks are carried out hourly for the first 4 hours, i.e. during their time in the emergency department. These are all carried out by a band 5 nurse.

Table A.6 summarises the cost of consumables used in carrying out IVT.

The model assumes that all children on IVT are admitted for an inpatient stay, where they complete IV treatment. This inpatient stay includes any costs of further treatment during the patient's stay in hospital. We use the costs of 'Infectious and non-infectious gastroenteritis without complications (non-elective)' as the NHS Healthcare Resource Group (HRG) code for this admission (Table A.7). The range of costs used for both base case and 'worst case' analysis is given in brackets.

Drip stands and infusion pumps are equipment pieces included in the costing of IVT and both of these are used for the 24 hour period of IVT. Costs for these are shown in Table A.8.

A number of blood tests are carried out when patients are treated with IVT and these are costed using a 'Pathology indicative tariff for haematology' from the NHS National Tariff and are shown in Table A.9.

Further IVT costing

The model assumes that if a child remains dehydrated after the initial 24 hours of IVT, treatment continues for another period of 24 hours. Patients receiving further treatment require additional resources. Further IVT requires a longer inpatient stay and the model assumes that the costs of this additional stay are given by the difference between the cost of a hospital episode for infectious and non-infectious gastroenteritis with complications and the cost without complications. This additional hospital stay is inclusive of any additional labour, consumables or equipment costs. Table A.10 summarises the hospital costs used in the analysis, and the range of costs used for both base case and 'worst case' analysis are given in brackets.

* In practice, most children are given less than 500 ml of saline. The smallest bag of saline available, however, is of 500 ml and once opened cannot be reused. The cost used in the analysis therefore is that of a 500 ml bag.

Table A.3 ORT labour costs

Task (staff)	Time taken (range) (min)	Unit cost	Cost (range)	Source
Patient education (band 5 nurse)	10 (10–20)	£30 per hour	£5.00 (£5.00–10.00)	Curtis ²⁰⁶
Patient review (band 5 nurse)	20 (20–30)	£30 per hour	£10.00 (£10.00–15.00)	Curtis ²⁰⁶
Clinical examination (specialty registrar)	10 (10–20)	£41 per hour	£6.83 (£6.83–13.67)	Curtis ²⁰⁶
Total labour costs			£21.83 (£21.83–38.66)	

Table A.4 ORT consumables costs

Variable	Quantity	Unit cost	Cost	Source
Dioralyte	2 sachets	£6.99 (20 sachet pack)	£0.70	BNF 55 (2008) ²⁰⁷
200 ml bottles ^a	2 bottles	£11.50 (pack of 42)	£0.55	NHS Supply Chain (2007) ²⁰⁸
Total consumables costs			£1.25	

^a Oral solution is often given to younger children via a syringe but as the cost difference between bottles and a syringe is small, the analysis has used the cost of bottles.

Table A.5 IVT labour costs

Task (staff)	Time taken (range)	No. times task carried out	Unit cost	Cost (range)	Source
Ametop® application (band 5 nurse)	5 minutes (1–5 minutes)	1	£30/hour	£2.50 (£0.50–2.50)	Curtis ²⁰⁶
Cannulation/taking blood samples:					
– 2 × band 5 nurse	Total of 35 minutes (0–35 minutes)	1	£30/hour	£17.50 (£0–17.50)	Curtis ²⁰⁶
– specialty registrar	17.5 minutes (N/A) ^a	1	£41/hour	£11.96 (N/A)	Curtis ²⁰⁶
Fluid preparation and attaching (2 × band 5 nurse)	Total of 15 minutes (10–15 minutes)	1	£30/hour	(£7.50) (£5.00–7.50)	Curtis ²⁰⁶
Baseline observations (band 5 nurse)	10 minutes per hour (5–10 minutes per hour)	4	£30/hour	£20.00 (£10.00–20.00)	Curtis ²⁰⁶
Equipment adjustment (band 5 nurse)	4 minutes per adjustment (N/A)	4	£30/hour	£8.00 (N/A)	Curtis ²⁰⁶
Site check (band 5 nurse)	5 minutes per check (N/A)	4	£30/hour	£10.00 (N/A)	Curtis ²⁰⁶
Total labour costs				£77.46 (£45.46–77.46)	

^a These values did not vary between base case and ‘worst case’ analyses.

Table A.6 IVT consumables costs

Variable	Quantity	Unit cost	Cost	Source
IV solution – sodium chloride (0.9% saline)	500 ml	£1	£1	www.baxterhealthcare.co.uk
Giving set with burette	2 (1 per 12 hours)	£1.75	£3.50	www.spsservices.co.uk
Fluid micron filter	1	£2.94	£2.94	NHS Supply Chain (2007)208
Cannula	2	£0.78	£1.56	NHS Supply Chain (2007) 208
Swabs	1 pack of 5	£0.05	£0.23	www.midmeds.co.uk
Alcohol skin prep	2	£0.01	£0.01	NHS Supply Chain (2007) 208
0.9% saline flushes	1 × 5 ml vial	£0.33	£0.33	BNFC (2007)209
Total consumable costs			£9.57	

Table A.7 IVT hospital costs

Hospital episode	Cost (range)	Source
Infectious and non-infectious gastroenteritis without complications	£602 (£365–602)	NHS Reference Costs (2006/07)

Table A.8 IVT equipment costs

Equipment	Duration	Lifespan	Unit cost	equivalent daily cost	Source
Infusion pump	24 hours	10 years	£100	£0.27	www.pasa.nhs.uk/PASAwab
Drip stand	24 hours	5 years	£105.16	£0.29	www.midmeds.co.uk
Total equipment costs				£0.56	

Table A.9 IVT test costs

Test	Quantity	Unit cost	Cost	Source
Full blood count and differential	1	£2.71	£2.71	Pathology indicative tariff for haematology, NHS National Tariff (2008/09)
Urea and electrolytes	1	£2.71	£2.71	Pathology indicative tariff for haematology, NHS National Tariff (2008/09)
Total test costs			£5.42	

Table A.10 Further IVT hospital costs

Hospital episode	Duration of stay	Cost (range)	Source
Infectious and non-infectious gastroenteritis with complications	2 days	£820 (£489–820)	NHS Reference Costs (2006/07)
Infectious and non-infectious gastroenteritis without complications	1 day	£602 (£365–602)	NHS Reference Costs (2006/07)
Inpatient further IVT stay	1 day	£218 ^a (£124)	

^a The 'Infectious and non-infectious gastroenteritis without complications' reference cost is for a 1 day stay in hospital and in this model has been attributed to the inpatient stay costs for providing IVT. Similarly, the reference costs for 'Infectious and non-infectious gastroenteritis with complications' is assumed to be the total costs for IVT and further IVT. The value of £820 is therefore the cost for a 2 day duration in hospital. In our model we have assumed that further IVT results in an extra 1 day stay in hospital and therefore in order to determine this cost we deducted 'Infectious and non-infectious gastroenteritis without complications' from 'Infectious and non-infectious gastroenteritis with complications' (£820 – £620 = £218) to avoid double counting. The same was done for the lower value of the range of costs.

Complications costing

It is thought that the majority of phlebitis resolves after the removal of the cannula. The costs of phlebitis are therefore attributed to the re-siting of the cannula and all associated equipment and staffing costs. Phlebitis costs are summarised in Table A.11. Potential antibiotic costs for the treatment have been excluded from the model. Extravasation injuries as a result of phlebitis have also been excluded from the model. The assumption made by the model is that the majority of these injuries will resolve themselves with no treatment.

The model assumes that if a patient is diagnosed with paralytic ileus they would be transferred to IVT and therefore the costs of paralytic ileus are encapsulated in the downstream cost of IVT and not as a separate cost.

Table A.11 Phlebitis costs

Item	Cost	Notes
Cannula	£0.78	
Staff tasks:	£8.42	It is assumed that re-siting the cannula and associated tasks take approximately 15 minutes. These tasks are done by nurses (band 5) and a specialty registrar.
• Ametop® application		
• cannulation and taking blood samples		
• fluid preparation/attaching		

‘Worst case’ sensitivity analysis

In addition to the base case analysis, a ‘worst case’ analysis for ORT relative to IVT has been considered. This was done in order to subject the findings of the base case model – that ORT was more cost-effective – to the most vigorous scrutiny by biasing model assumptions, within plausible limits, in favour of IVT. By carrying out a ‘worst case’ analysis, it is possible to determine whether or not ORT remains the most cost-effective option even under assumptions that are intended to represent the least favourable scenario for ORT.

Parameters changed for ORT

For this ‘worst case’ sensitivity analysis, the following changes were made:

Probabilities

For point estimates of proportions, the upper limit of the 95% confidence intervals were calculated to obtain the highest probability of:

- failure to rehydrate following ORT
- paralytic ileus following ORT.

The implication of doing this is a higher percentage of patients failing ORT and therefore a higher level of hospitalisation within ORT.

Staff

The GDG were asked to estimate the maximum time it could take staff to carry out ORT-related tasks. These time values were used to calculate the maximum costs for labour for ORT (see Table A.3).

Parameters changed for IVT

The ‘worst case’ favoured IVT and therefore the aim here was to cost up a much less resource-intensive means of providing IVT. The following changes were made:

Probabilities

To try to make the best case for IVT, the probability of failing to hydrate following IVT and the probability of complications (namely phlebitis) following IVT were changed to 0.

Staff

The ‘worst case’ analysis used the minimum time that staff could take in order to complete IVT-related tasks. Again, these times were estimated by the GDG and represent a relatively low-cost method of delivering IVT (see Table A.4).

Hospital costs

Reference costs report both upper and lower quartile values for costs of hospital stay in addition to the national average. The lower quartiles for inpatient IV and further IV stay were used in order to keep the total costs of delivering IVT to the lowest possible value (see Table A.7).

Results

The results for the baseline and ‘worst case’ analysis are presented in Tables A.12 and A.13, respectively.

Table A.12 Baseline analysis – cost of each strategy and threshold QALY gain necessary for cost-effectiveness

Strategy	Cost	Incremental cost	Incremental QALY gain needed
ORT	£71.08		
IVT	£701.56	£630.48	0.032

Table A.13 ‘Worst case’ sensitivity analysis – cost of each strategy and threshold QALY gain necessary for cost-effectiveness

Strategy	Cost	Incremental cost	Incremental QALY gain needed
ORT	£74.17		
IVT	£426.01	£351.84	0.018

In Tables A.12 and A.13, the two strategies are ranked in terms of cost, least costly first. With both therapies, the model assumes that all patients are hydrated within a given time frame and, because of this, effectiveness is assumed to be equivalent for both treatments. The third column gives the cost differential between the two treatments. Clearly, if the two treatments are equally effective in all respects, then ORT, as the cheaper option, is considered cost-effective.

Using the costs of the two strategies we can undertake a form of ‘what-if’ or threshold analysis. If we have accurately captured the *opportunity cost* of the two strategies, then the values in the final column of Tables A.12 and A.13 are indicative of the incremental QALY gain needed in order for the treatment to be considered a cost-effective option in comparison with the next cheapest option. In the base case analysis, if IVT provided at least 0.032 QALYs more than ORT, IVT would be considered cost-effective relative to ORT using NICE criteria. Similarly in the ‘worst case’ analysis, IVT would need to provide a minimum of a 0.018 QALY gain in order for it to be considered cost-effective.

This incremental QALY calculation is derived by dividing the incremental cost by £20,000. This is the value NICE adopts as its willingness to pay benchmark for cost-effectiveness and is obtained from the NICE *Guidelines Manual*.²¹⁰

One-way sensitivity analysis

Sensitivity analysis is used in economic evaluation to assess how sensitive the results of the model are to the assumptions made about the model parameters, particularly those parameters where considerable uncertainty exists as to their actual value. One-way sensitivity analysis involves altering the value of a single parameter, holding all the others constant*, to determine how sensitive the cost-effectiveness conclusion is to the assumptions made about that particular parameter.

* For these analyses it is base case values that are kept constant.

Figure A.2 shows the one-way sensitivity analysis for the probability of phlebitis. This probability is ranged from 1 to 10% to illustrate how this changes the incremental costs of IVT. Figure A.3 shows the one-way sensitivity analysis for the probability of paralytic ileus, again ranging from 1 to 10%. Finally, Figure A.4 shows the one-way sensitivity analysis with varying costs of ORT (this can be considered equivalent to a sensitivity analysis varying the cost differential between ORT and IVT).

Multi-way sensitivity analysis is where several parameters values are changed simultaneously, although one of the difficulties with this technique is the huge number of possible permutations that may exist. An alternative method to evaluate the uncertainty across several model parameters is to use a technique called probabilistic sensitivity analysis (PSA). This involves setting a

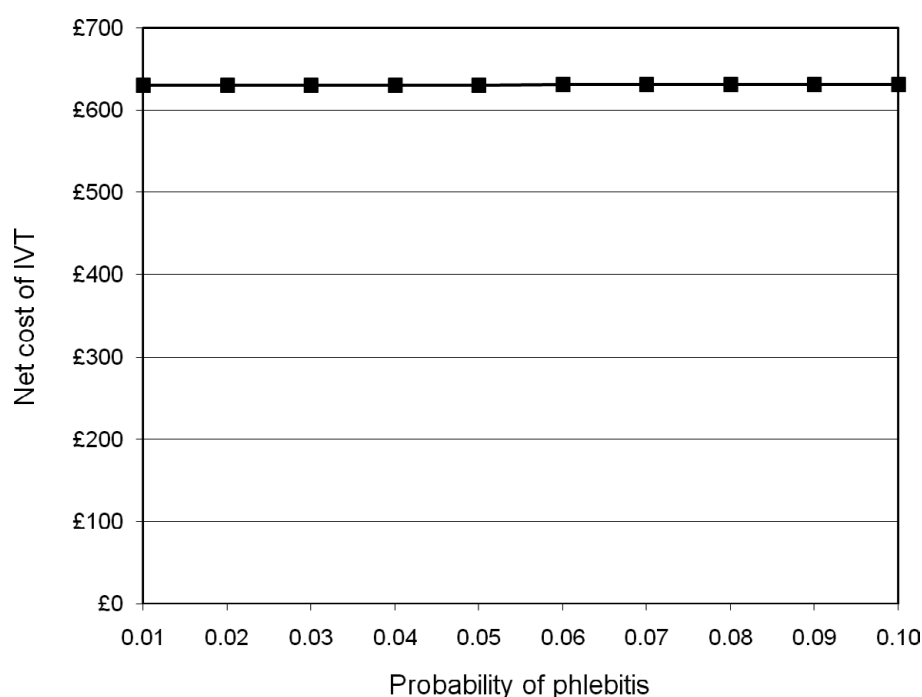


Figure A.2 One-way sensitivity analysis varying the probability of phlebitis as a complication of IVT

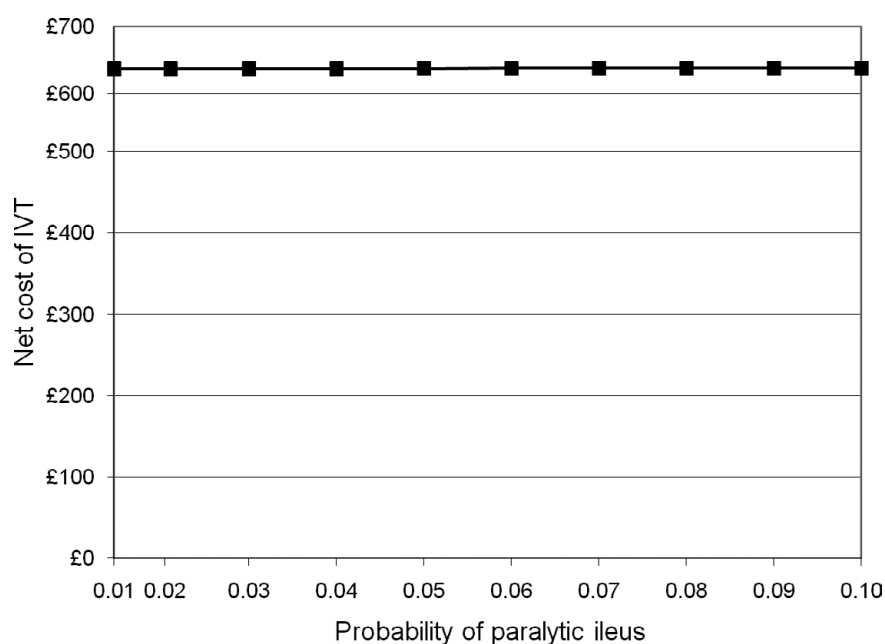


Figure A.3 One-way sensitivity analysis varying the probability of paralytic ileus

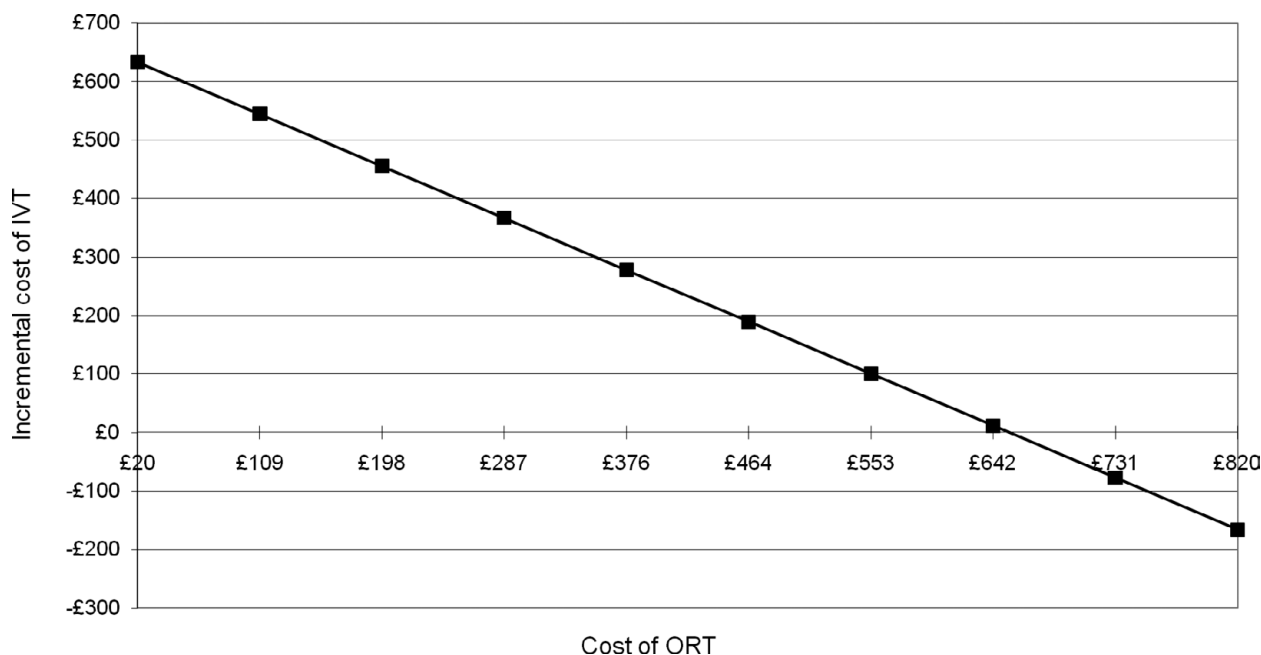


Figure A.4 One-way sensitivity analysis varying the cost of ORT

probability distribution for some or all model parameters. A Monte Carlo simulation is then run, which involves running the model many times over, where probabilistic parameter values are sampled randomly from their probability distribution on each run.

For the PSA undertaken for this paper, we restricted the probabilistic parameters to those that were derived from the Cochrane review.* In the deterministic analysis, a point estimate was taken from the Cochrane review. However, such point estimates are always subject to inherent sampling errors. This is the basis of inferential statistics and is at the heart of the hypothesis tests used to test for differences and the calculations of confidence intervals. The probability distribution for the model parameters acknowledges this sampling uncertainty while using the point estimate as the 'best guess' of the true value. A 'beta distribution' was chosen for each of the probabilistic parameters. This is similar to the normal distribution but is constrained to an interval between 0 and 1, a necessary requirement for probability parameters. For this PSA, 100 Monte Carlo simulations were run and the results are shown in Figure A.5.

In this analysis, the probability of ORT being cheaper than IVT was 100%.

Discussion

The baseline result shown in Table A.12 suggests that, when 'downstream' costs[†] are considered, ORT is £630.48 cheaper than IVT. Table A.13 shows that, in the 'worst case' sensitivity analysis, ORT is £351.84 cheaper than IVT.

The model that has been developed is essentially a cost-minimisation analysis. The model assumes that all patients rehydrate even if at some stage they are classified as treatment 'failures'. Using rehydration as the measure of outcome means that the treatment alternatives do not vary in terms of their effectiveness and therefore the cheapest option is also unambiguously the most cost-effective.

Of course, while it may be a reasonable approximation to assume equivalent effectiveness (and hence a reasonable model assumption), in practice there are differences between the two treatments. Firstly, the meta-analysis undertaken for the Cochrane review was not powered to detect rare adverse events. It may be that there are rare but clinically important harms that do differ systematically between the two treatment alternatives. Secondly, the Cochrane review did show a higher rate of treatment 'failure' for ORT. It seems likely that such treatment failure

* Other model parameters were held constant as in the deterministic baseline analysis.

† Costs which are incurred as a result of the treatment but subsequent to it, e.g. costs arising from treatment complications.

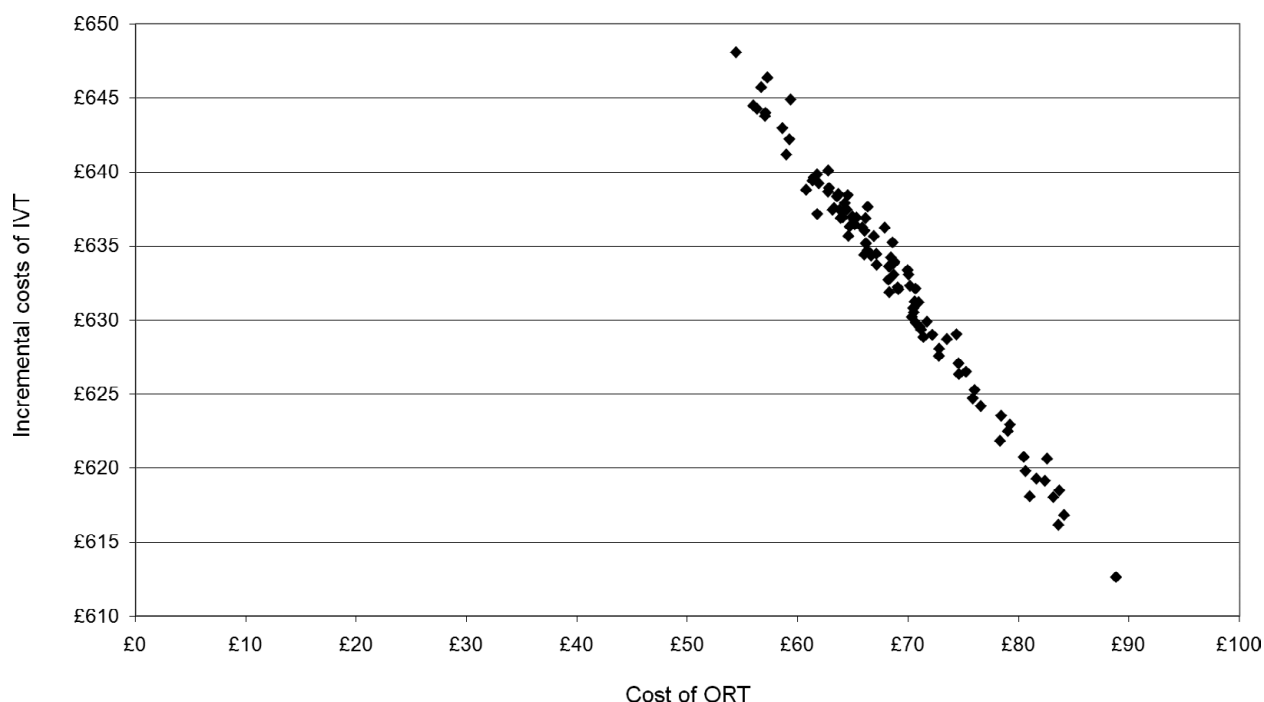


Figure A.5 Monte Carlo simulation showing the incremental costs of IVT against the cost of ORT

would be associated with a longer period of symptoms and morbidity. On the other hand, the review also presented evidence suggesting that IVT was associated with a statistically significant increase in length of hospital stay, which might partly reflect increased morbidity and could have a negative impact itself in terms of cross-infection. Furthermore, it was stated in the Cochrane review that 'IVT is a traumatic experience for most children' and therefore this may be another difference, albeit small, between the treatments in terms of their impact on quality of life.

To allow for the possibility that the treatments are not equally efficacious, the results in Tables A.12 and A.13 are presented with a threshold for QALY gain if IVT is to be considered cost-effective. If, taking into account all other factors, including those mentioned above, ORT also gives the greatest QALY gain then this simply strengthens the cost-effectiveness implied by the cost-minimisation analysis. However, if IVT were judged to be the better clinical alternative then the results of the threshold analysis suggests that, in the base case, IVT could be considered cost-effective if it delivered a gain of at least 0.032 QALYs over and above that which would be obtained using ORT. Similarly, for the 'worst case' analysis the QALY gain needed for IVT to be considered cost-effective would need to be 0.018. This is based on a willingness to pay of £20,000 per QALY, which is a threshold for cost-effectiveness set by NICE.

How likely is it that that such a QALY gain would be attained? An intervention which added a year of life lived in perfect health would give an incremental gain of 1 QALY. Hence, an intervention that gave an additional day of life lived in perfect health therefore would yield an incremental gain of 0.003 QALYs. Therefore, it seems unlikely for the cost differences in these analyses that IVT would be considered cost-effective. The success of rehydration therapy is usually measured in hours not days and the incremental QALY weight attached to a state of rehydration compared with dehydration is likely to be much less than 1.

The sensitivity analysis illustrated in Figures A.2 and A.3 shows that the results are not very sensitive to changes in the probability of phlebitis with IVT or the probability of paralytic ileus with ORT. An important driver of this in the model is the relatively low cost assumed to be associated with such events. If the costs associated with such complications were much higher than that implied by the model then changes to these probabilities would have a bigger effect on the final cost-effectiveness conclusions.

The sensitivity analysis depicted in Figure A.4 shows, unsurprisingly, that the cost-minimisation results are sensitive to the cost of ORT (or, more accurately, the cost differential between the two treatment alternatives). The analysis shows that, as long as the initial ORT treatment cost is less than £653 (or its initial treatment cost is at least £48 cheaper than the initial treatment cost for IVT), then it remains the cheapest option even when considering 'downstream' costs.

The PSA in Figure A.5 suggests that there is a 100% probability that ORT is the cheapest option. Unsurprisingly, the graph shows a negative relationship between the cost of ORT and the incremental costs of IVT (as the latter is a function of the former). In the PSA simulations, ORT is relatively more expensive when higher treatment failure values and/or higher rates of paralytic ileus are sampled. Similarly, the cost of IVT may also vary depending on the sampled failure rate of treatment and the probability of phlebitis.

The results of the 'worst case' sensitivity analysis show that, even in the least favourable circumstances, ORT remains the more cost-effective option, therefore strengthening the case for its use in the treatment of dehydrated children.

Appendix B

Health economics of ondansetron

Introduction

Children presenting with acute gastroenteritis often have high levels of vomiting. There is currently no widely accepted method of treatment for the cessation of vomiting in such patients in the UK. Vomiting is not only distressing to both patients and their families but can also interfere with the oral rehydration process and can limit the success of oral rehydration therapy (ORT). Children who are unable to tolerate rehydration fluids orally are then given intravenous fluid therapy (IVT), which in turn has additional significant resource implications. It is thought that the use of anti-emetics may be effective in the cessation of vomiting and may in turn help with the successful delivery of ORT, thereby reducing the need to treat with IVT. Consequently, this would have cost saving implication for the NHS through fewer admissions for IVT. Ondansetron is recognised as an effective anti-emetic and is used frequently in post-operative patients and also in oncology. The GDG felt that an economic analysis would help guide recommendations regarding its use.

Economic analysis

A literature review identified several articles investigating the effectiveness of ondansetron in children with vomiting due to gastroenteritis. The evidence was for both oral and IV uses of ondansetron but the evidence for the efficacy of IV ondansetron was limited and thus the economic analysis only considers oral administration. None of the articles retrieved included any data regarding costs or cost-effectiveness.

A simple economic model was constructed to assess the cost-effectiveness of ondansetron. The model probabilities are taken from a meta-analysis that pooled the results of three RCTs^{160,163,164} comparing the effects of administration of oral ondansetron against placebo in children with vomiting. Model probabilities are presented in Table B.1. The three main outcomes considered are:

- cessation of vomiting
- need for IVT
- hospitalisation.

Model costs are taken from the decision analytical model for the cost-effectiveness of IVT versus ORT for children with dehydration (Appendix A). All cost inputs are presented in Table B.2. The cost for ondansetron was obtained from the *British National Formulary for Children* (BNFC 2007).²⁰⁹ It is assumed that only one dose of ondansetron (at a strength of 4 mg) is given to the vomiting patient.

The effectiveness of ondansetron is measured by an increase in the cessation of vomiting. The need for further IVT and hospitalisation are both measures of resource use subsequent to treatment. To

Table B.1 Model probabilities

Outcome	Control	Distribution	Ondansetron	Distribution
Cessation of vomiting ^a	0.652	Beta ($\alpha = 116, \beta = 62$)	0.862	Beta ($\alpha = 156, \beta = 25$)
Hospitalisation	0.099	Beta ($\alpha = 23, \beta = 210$)	0.039	Beta ($\alpha = 9, \beta = 223$)
Need for IV treatment	0.339	Beta ($\alpha = 79, \beta = 154$)	0.137	Beta ($\alpha = 30, \beta = 189$)

^a The outcome of 'cessation of vomiting' was only reported in two of the trials.^{163,164}

the extent that ondansetron leads to lower hospitalisation and need for IVT, there will be savings to at least partially offset some of the costs of treatment.

The analysis calculates the difference in effect between placebo and ondansetron for the three outcomes from the pooled meta-analysis. Any savings in potential downstream costs is then calculated and this is attributed to the difference in effect achieved by taking a dose of ondansetron. This downstream saving is calculated by multiplying the difference in effect by the costs of treatment. It is also important to note that this saving also needs to be offset against the cost of treatment, i.e. the cost of ondansetron. Therefore:

Net savings = downstream savings – treatment cost of ondansetron

Results

The results of the analysis are listed in Table B.3. Note that the outcome of ‘cessation of vomiting’ was only reported in two of the trials.^{163,164} Net savings are derived by multiplying the difference in effect by the costs of treatment.

Once the treatment cost is taken into account, this gives a net saving of approximately £52 with ondansetron compared with placebo. Given that ondansetron also leads to a benefit in terms of increased cessation of vomiting, this implies that the treatment is dominant, providing additional clinical benefit at reduced cost.

Sensitivity analysis

It is important in economic evaluation to take into account uncertainty. Therefore, a probabilistic sensitivity analysis (PSA) was undertaken to reflect the fact that the meta-analysis only provides an estimate of the ‘true’ effect size. To carry out the PSA, the model was run for 10 000 simulations with the values of the model probabilities sampled from a probability distribution, as indicated in Table B.1. The cost values were accepted as fixed as these are based on published cost data. The results of the probabilistic simulations are shown in Figure B.1.

Table B.2 Costs used in the model

Item	Value	Source
Ondansetron	£3.24	<i>British National Formulary for Children</i> (BNFC 2007) ²⁰⁹
IVT	£93.01 ^a	Cost-effectiveness of IVT versus ORT for children with dehydration (Appendix A)
Hospitalisation	£602.00	Cost-effectiveness of IVT versus ORT for children with dehydration (Appendix A)

^a This value of £93.01 is obtained by summing all costs (equipment, labour, tests and consumables) derived for IVT in Appendix A.

Table B.3 Net savings with ondansetron using the pooled meta-analysis

Outcome	Probabilities			Net savings with ondansetron
	Control	Ondansetron	Difference in effect	
Cessation of vomiting	0.652	0.862	0.210	N/A ^a
Hospitalisation	0.099	0.039	0.060	£36.12
Need for IVT	0.137	0.339	0.202	£18.79
Total downstream savings				£54.91
Total net savings				£51.68

^a Vomiting has been assumed to have no associated costs and therefore no savings are made by the cessation of vomiting.

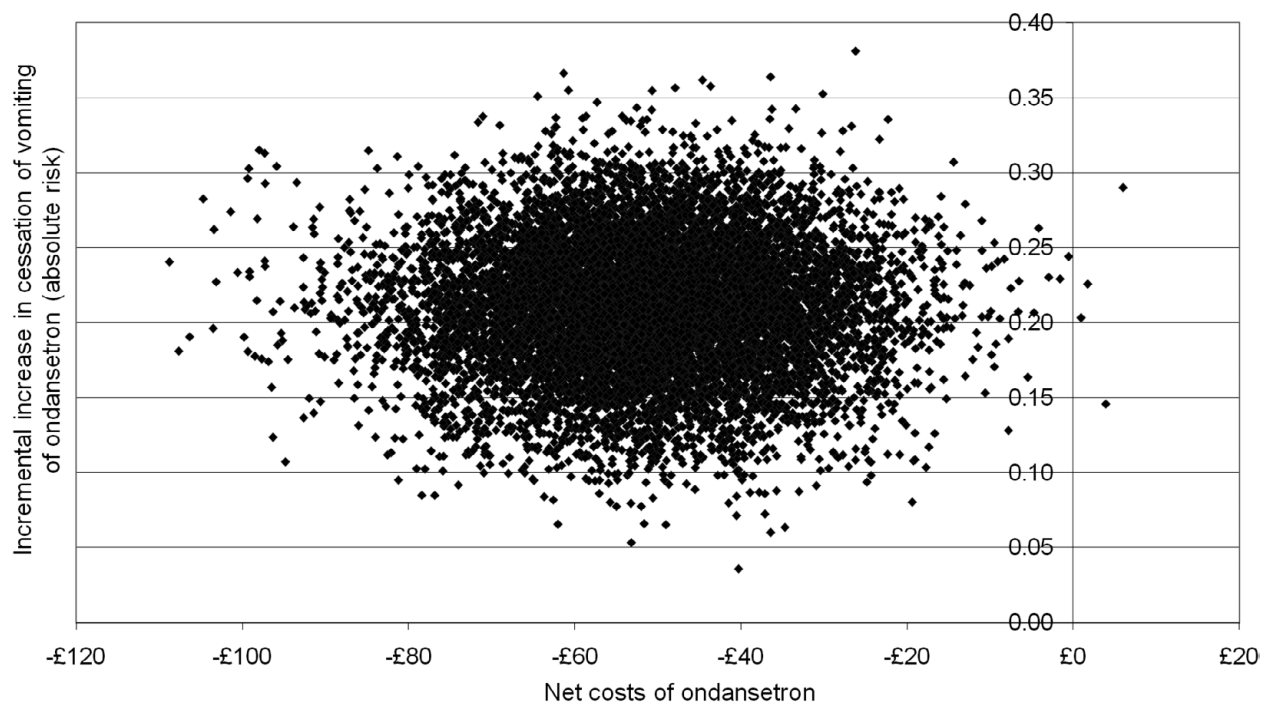


Figure B.1 Probabilistic sensitivity analysis of the net costs and effects of ondansetron ($n = 10\,000$)

The PSA results showed that in every simulation ondansetron led to a greater cessation in vomiting than placebo, providing very strong evidence for the efficacy of the intervention. It also showed ondansetron to be cost saving in 99.96% of simulations,

Discussion

The baseline result shows that ondansetron is dominant compared with placebo, with increased cessation of vomiting and a net saving of £51.68. A PSA suggested this cost-effectiveness conclusion was not sensitive to parameter uncertainty in the model's probabilities. This is because the magnitudes of the effect sizes for cessation of vomiting and reduced resources are so large (and the confidence intervals sufficiently narrow) that they are most unlikely to be due to chance. As the costs of hospitalisation and IVT are high relative to treatment, a real reduction in the costs associated with these events is likely to offset the initial ondansetron drug cost.

There are a number of caveats to be considered when interpreting the above results. Firstly, the PSA assumed independence in the three probabilistic model parameters. In practice, it would be expected that a reduction in hospitalisation and IVT is dependent on the efficacy of ondansetron. Therefore, a more sophisticated model would demonstrate an inverse relationship between the net costs of ondansetron and increased cessation of vomiting. Nevertheless, the importance of this should not be overstated. As the independent variable, the distribution of cessation of vomiting rates is not affected by the assumption of independence. Although a more sophisticated model may show a greater uncertainty around the mean net costs, the efficacy of the intervention would still be likely to produce some offsetting savings and the probability of a net cost saving would remain high.

The two studies that reported the outcome of 'cessation of vomiting' occurring 'a few hours' after ondansetron is taken use different time frames from each other. One study¹⁶³ looked at the proportion of children who vomited while receiving ORT whereas the other¹⁶⁴ measured the frequency of emesis during the 48 hour period after enrolment. All the studies in the meta-analysis were undertaken in the USA and treatment practice differs in England and Wales. In the NHS, a child would be admitted as an inpatient if their vomiting had not stopped within 4 hours of taking ondansetron in the emergency department, regardless of whether the child ultimately receives IVT. This inpatient admission would incur costs. Therefore, the time frame used in the

US studies may not be the most relevant to UK practice, particularly with respect to subsequent resource use. It cannot be assumed that the savings imputed from US models of care would be transferable to an NHS setting.

The inclusion criteria for the studies included in the meta-analysis also varied. One study¹⁶³ included children with at least one reported episode of vomiting within the 4 hours preceding triage whereas another¹⁶⁴ enrolled patients with five episodes of vomiting in the preceding 24 hours. The authors felt that the inclusion criteria for those being given ondansetron should be restrictive in order to best identify the group of patients who would benefit from ondansetron. This is in line with the view of the GDG who also agreed that not every child should be given ondansetron but only those who are most likely to benefit, i.e. those patients who would otherwise fail ORT and go on to IVT. It is in this group of patients that savings could be made.

None of the three above-mentioned studies reported any significant adverse events or complicating side effects from the use of ondansetron and the economic analysis has not taken into these into account. Nevertheless, the BNFC²⁰⁹ reports several possible side effects from ondansetron, ranging from headaches to chest pain and seizures. The chance of these side effects occurring, although small, could lower the health-related quality of life improvement of ondansetron. It is therefore important to remember the importance of any potential harms that may be of clinical importance and may differ systematically between those who are treated with ondansetron and those who are not.

Changes in diarrhoea in response to treatment was not included in this model because it was unclear whether ondansetron worsened this outcome and more importantly because the GDG queried the clinical significance of diarrhoeal outcomes reported in the studies. Two trials in the meta-analysis^{163,164} reported a statistically significant increase in the frequency of diarrhoea as an adverse event of ondansetron. A third study¹⁶⁰ showed that the number of children with fewer episodes of diarrhoea was less with ondansetron but the difference was not statistically significant. To more accurately determine the cost-effectiveness of ondansetron, it would be important to know the clinical significance of any increased diarrhoea and whether it led to a concomitant increase in the use of healthcare resources.

In the economic model, it was assumed patients are given a single oral dose of ondansetron in order to reduce vomiting. This is consistent with two of the studies included in the meta-analysis.^{163,211} However, the third study¹⁶⁴ gave a single oral dose of ondansetron in hospital but also provided discharged patients with an additional five doses of ondansetron to be used every 8 hours for a total of 2 days. Although this approach would increase the cost of ondansetron, repeated home doses of ondansetron may also help in delivering persistent benefit and consistently reduce hospital admission. This would clearly have implications for the economic analysis.

Finally, treatment costs were restricted to the cost of ondansetron. To the extent that other costs, such as staffing, in administering oral ondansetron have been omitted, there will be a bias, albeit small, in favour of ondansetron in this analysis.

Although ORT has been proven to be a clinically effective and cost-effective treatment for children suffering from dehydration, it remains underused, especially when the child is vomiting. Clinicians are more likely to choose IVT in scenarios where vomiting is a major symptom, and therefore a safe and effective method of controlling vomiting, such as ondansetron, may increase the use of ORT. The simple model in this appendix is suggestive of potential clinical and economic benefits of ondansetron; however, more evidence, particularly with regard to diarrhoeal outcomes, was felt to be necessary by the GDG to justify its use in routine practice.

References

1. World Health Organization. *The World Health Report 2007 – a Safer Future: Global Public Health Security in the 21st Century*. Geneva: WHO; 2007.
2. Bryce J, Boschi-Pinto C, Shibuya K, et al. WHO estimates of the causes of death in children. *Lancet* 2005;365:1147–52.
3. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bulletin of the World Health Organization* 2003;81:197–204.
4. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *Journal of Health Population and Nutrition* 2001;19:339–46.
5. Practice parameter: the management of acute gastroenteritis in young children. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. *Pediatrics* 1996;97:424–35.
6. Van DP, Giaquinto C, Huet F, et al. Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *Journal of Infectious Diseases* 2007;195 Suppl 1:S4–S16.
7. Lorgelly PK, Joshi D, Iturriza GM, et al. Infantile gastroenteritis in the community: a cost-of-illness study. *Epidemiology and Infection* 2008;136:34–43.
8. Fischer TK, Viboud C, Parashar U, et al. Hospitalizations and deaths from diarrhea and rotavirus among children <5 years of age in the United States, 1993–2003. *Journal of Infectious Diseases* 2007;195:1117–25.
9. The Pediatric ROTavirus European Committee (PROTECT). The paediatric burden of rotavirus disease in Europe. *Epidemiology and Infection* 2006;134:908–16.
10. Charles MD, Holman RC, Curns AT, et al. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993–2002. *Pediatric Infectious Disease Journal* 2006;25:489–93.
11. Wheeler JG, Sethi D, Cowden JM, et al. Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. The Infectious Intestinal Disease Study Executive. *British Medical Journal* 1999;318:1046–50.
12. Armon K, Stephenson T, Gabriel V, et al. Audit: Determining the common medical presenting problems to an accident and emergency department. *Archives of Disease in Childhood* 2001;84:390–2.
13. Lopez-de-Andres A, Jimenez-Garcia R, Carrasco-Garrido P, et al. Hospitalizations associated with rotavirus gastroenteritis in Spain, 2001–2005. *BMC Public Health* 2008;8:109.
14. Lopman BA, Reacher MH, Vipond IB, et al. Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002–2003. *Emerging Infectious Diseases* 2004;10:1827–34.
15. Bucher B, Aebi C. Population-based epidemiology of rotavirus hospitalisations in Switzerland. *Swiss Medical Weekly* 2006;136:726–31.
16. Murphy MS. Guidelines for managing acute gastroenteritis based on a systematic review of published research. *Archives of Disease in Childhood* 1998;79:279–84.
17. Armon K, Stephenson T, MacFaul R, et al. An evidence and consensus based guideline for acute diarrhoea management. *Archives of Disease in Childhood* 2001;85:132–42.
18. Duggan C, Santosham M, Glass RI. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report. Recommendations and Reports* 1992;41(RR-16):1–20.
19. King CK, Glass R, Bresee JS, et al.; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR: Morbidity and Mortality Weekly Report* 2003;52:1–16.
20. World Health Organization. *The Treatment of Diarrhoea: a Manual for Physicians and Other Senior Health Workers*. 4th ed. Geneva: WHO; 2005.
21. Bhatnagar S, Lodha R, Choudhury P, et al. IAP Guidelines 2006 On Management of Acute Diarrhea. *Indian Pediatrics* 2007;44:380–9.
22. European Society for Paediatric Gastroenterology HaN and European Society for Paediatric Infectious Diseases. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. *Journal of Pediatric Gastroenterology and Nutrition* 2008;46 Suppl 2:S81–122.
23. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine. How to Practice and Teach EBM*. London: Churchill-Livingstone; 1997. p. 167.
24. Szajewska H, Hoekstra JH, Sandhu B. Management of acute gastroenteritis in Europe and the impact of the new recommendations: a multicenter study. The Working Group on acute Diarrhoea of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2000;30:522–7.
25. NHS Executive. *Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS*. London: HMSO; 1996.
26. National Institute for Health and Clinical Excellence. *The Guidelines Manual*. London: National Institute for Health and Clinical Excellence; 2009.
27. Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1993;270:2093–5.
28. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1993;270:2598–601.
29. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1994;271:59–63.
30. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1994;271:389–91.
31. Jordan R, Law M. An appraisal of the efficacy and cost effectiveness of antenatal screening for hepatitis B. *Journal of Medical Screening* 1997;4:117–27.

32. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine. How to Practice and Teach EBM*. 2nd ed. Edinburgh: Churchill Livingstone; 2000.
33. Scottish Intercollegiate Guidelines Network. *A Guideline Developers' Handbook*. No. 50. Edinburgh: SIGN; 2001.
34. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press; 1997.
35. Drummond MF, Sculpher M, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. Oxford: Oxford University Press; 2005.
36. Personal communication from Simon Minford, GDG member. 2008.
37. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, et al.; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. *Clinical Infectious Diseases* 2001;32:331–51.
38. World Health Organization. *Diarrhoea Treatment Guidelines for Clinical Based Healthcare Workers*. Geneva: WHO; 2005.
39. Feldman M. Nausea and vomiting. In: Sleisenger MH, Fordtran JS, editors. *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. 4th ed. Philadelphia: W.B. Saunders Co.; 1989. p. 222–38.
40. Szymanski H, Pejcz J, Jawien M, et al. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains—a randomized, double-blind, placebo-controlled trial. *Alimentary Pharmacology and Therapeutics* 2006;23:247–53.
41. Gazala E, Weitzman S, Weizman Z, et al. Early vs. late refeeding in acute infantile diarrhea. *Israel Journal of Medical Sciences* 1988;24:175–9.
42. Lozano JM, Cespedes JA. Lactose vs. lactose free regimen in children with acute diarrhoea: a randomized controlled trial. *Archivos Latinoamericanos de Nutricion* 1994;44:6–11.
43. Haffejee IE. Cow's milk-based formula, human milk, and soya feeds in acute infantile diarrhea: a therapeutic trial. *Journal of Pediatric Gastroenterology and Nutrition* 1990;10:193–8.
44. Khuffash FA, Sethi SK, Shaltout AA. Acute gastroenteritis: clinical features according to etiologic agents. *Clinical Pediatrics* 1988;27:365–8.
45. Rosenfeldt V, Michaelsen KF, Jakobsen M, et al. Effect of probiotic Lactobacillus strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. *Pediatric Infectious Disease Journal* 2002;21:417–9.
46. Dugdale A, Lovell S, Gibbs V, et al. Refeeding after acute gastroenteritis: a controlled study. *Archives of Disease in Childhood* 1982;57:76–8.
47. Haque KN, al-Frayh A, el-Rifai R. Is it necessary to regraduate milk after acute gastroenteritis in children? *Tropical and Geographical Medicine* 1983;35:369–73.
48. Isolauri E, Vesikari T, Saha P, et al. Milk versus no milk in rapid refeeding after acute gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 1986;5:254–61.
49. Rees L, Brook CG. Gradual reintroduction of full-strength milk after acute gastroenteritis in children. *Lancet* 1979;1:770–1.
50. Armitstead J, Kelly D, Walker-Smith J. Evaluation of infant feeding in acute gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 1989;8:240–4.
51. Uhnoo I, Olding-Stenkvist E, Kreuger A. Clinical features of acute gastroenteritis associated with rotavirus, enteric adenoviruses, and bacteria. *Archives of Disease in Childhood* 1986;61:732–8.
52. Colomba C, De GS, Giammanco GM, et al. Viral gastroenteritis in children hospitalised in Sicily, Italy. *European Journal of Clinical Microbiology and Infectious Diseases* 2006;25:570–5.
53. Conway SP, Phillips RR, Panday S. Admission to hospital with gastroenteritis. *Archives of Disease in Childhood* 1990;65:579–84.
54. Deivanayagam N, Mala N, Ashok TP, et al. Risk factors for persistent diarrhea among children under 2 years of age. Case control study. *Indian Pediatrics* 1993;30:177–85.
55. Cheney CP, Wong RK. Acute infectious diarrhea. *Medical Clinics of North America* 1993;77:1169–96.
56. National Collaborating Centre for Women's and Children's Health. *Feverish Illness in Children. Assessment and Initial Management in Children Younger Than 5 Years*. London, RCOG Press; 2007.
57. Ellis ME, Watson B, Mandal BK, et al. Contemporary gastroenteritis of infancy: clinical features and prehospital management. *British Medical Journal* 1984;288:521–3.
58. Jenkins HR, Ansari BM. Management of gastroenteritis. *Archives of Disease in Childhood* 1990;65:939–41.
59. Froggatt PC, Vipond IB, Ashley CR, et al. Surveillance of norovirus infection in a study of sporadic childhood gastroenteritis in South West England and South Wales, during one winter season (1999–2000). *Journal of Medical Virology* 2004;72:307–11.
60. Cunliffe NA, Allan C, Lowe SJ, et al. Healthcare-associated rotavirus gastroenteritis in a large paediatric hospital in the UK. *Journal of Hospital Infection* 2007;67:240–4.
61. Van DP, Giaquinto C, Maxwell M, et al. Distribution of rotavirus genotypes in Europe, 2004–2005: the REVEAL Study. *Journal of Infectious Diseases* 2007;195 Suppl 1:S17–S25.
62. Gomara MI, Simpson R, Perault AM, et al. Structured surveillance of infantile gastroenteritis in East Anglia, UK: Incidence of infection with common viral gastroenteric pathogens. *Epidemiology and Infection* 2008;136:23–33.
63. Health Protection Agency. *Laboratory Reports of Faecal Isolates Reported to the Health Protection Agency Centre for Infections By Age England and Wales, 1992–2006*. London: Health Protection Agency; 2008 [www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/119573381191919?p=1191942150126].
64. Travel and Migrant Health Section, Health Protection Agency. *Foreign Travel-Associated Illness: England, Wales, and Northern Ireland – Annual Report 2005*. London: HPA; 2005.
65. Borgnolo G, Barbone F, Guidobaldi G, et al. C-reactive protein in viral and bacterial gastroenteritis in childhood. *Acta Paediatrica* 1996;85:670–4.
66. Lin CH, Hsieh CC, Chen SJ, et al. The diagnostic value of serum interleukins 6 and 8 in children with acute gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 2006;43:25–9.
67. Marcus N, Mor M, Amir L, et al. The quick-read C-reactive protein test for the prediction of bacterial gastroenteritis in the pediatric emergency department. *Pediatric Emergency Care* 2007;23:634–7.
68. Ashkenazi S, Amir Y, Dinari G, et al. Differential leukocyte count in acute gastroenteritis. An aid to early diagnosis. *Clinical Pediatrics* 1983;22:356–8.
69. Bhattacharya SK, Bhattacharya MK, Manna B, et al. Risk factors for development of dehydration in young children with acute watery diarrhoea: a case-control study. *Acta Paediatrica* 1995;84:160–4.
70. Zodepy SP, Deshpande SG, Ughade SN, et al. Risk factors for development of dehydration in children aged under five who have acute watery diarrhoea: a case-control study. *Public Health* 1998;112:233–6.

71. Victora CG, Fuchs SC, Kirkwood BR, *et al.* Breast-feeding, nutritional status, and other prognostic factors for dehydration among young children with diarrhoea in Brazil. *Bulletin of the World Health Organization* 1992;70:467–75.
72. Fuchs SC, Victora CG, Martines J. Case-control study of risk of dehydrating diarrhoea in infants in vulnerable period after full weaning. *British Medical Journal* 1996;313:391–4.
73. Ahmed FU, Karim E. Children at risk of developing dehydration from diarrhoea: a case-control study. *Journal of Tropical Pediatrics* 2002;48:259–63.
74. Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? *JAMA: the Journal of the American Medical Association* 2004;291:2746–54.
75. Shavit I, Brant R, Nijssen-Jordan C, *et al.* A novel imaging technique to measure capillary-refill time: improving diagnostic accuracy for dehydration in young children with gastroenteritis. *Pediatrics* 2006;118:2402–8.
76. World Health Organization. *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources*. Geneva: WHO; 2005.
77. Sandhu BK; European Society of Pediatric Gastroenterology, Hepatology and Nutrition Working Group on Acute Diarrhoea. Practical guidelines for the management of gastroenteritis in children. *Journal of Pediatric Gastroenterology and Nutrition* 2001;33 Suppl 2:S36–9.
78. Hill ID, Mann MD, Bowie MD. Hypernatraemic dehydration. A prospective study in children with diarrhoeal disease. *South African Medical Journal* 1981;59:479–81.
79. Yurdakok K, Oran O. The relationship between blood glucose and serum electrolyte levels in children with acute diarrhea. *Turkish Journal of Pediatrics* 1992;34:145–52.
80. Reid SR, Losek JD. Hypoglycemia complicating dehydration in children with acute gastroenteritis. *Journal of Emergency Medicine* 2005;29:141–5.
81. Steiner MJ, Nager AL, Wang VJ. Urine specific gravity and other urinary indices: inaccurate tests for dehydration. *Pediatric Emergency Care* 2007;23:298–303.
82. Faruque AS, Mahalanabi D, Islam A, *et al.* Breast feeding and oral rehydration at home during diarrhoea to prevent dehydration. *Archives of Disease in Childhood* 1992;67:1027–9.
83. Hartling L, Bellemare S, Wiebe N, Russell K, Klassen TP, Craig W. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database of Systematic Reviews* 2006;3:CD004390.
84. Hidayat S, Srie Enggar KD. Nasogastric drip rehydration therapy in acute diarrhea with severe dehydration. *Paediatrica Indonesiana* 1988;28:79–84.
85. Sharifi J, Ghavami F, Nowrouzi Z, *et al.* Oral versus intravenous rehydration therapy in severe gastroenteritis. *Archives of Disease in Childhood* 1985;60:856–60.
86. Snyder JD. Use and misuse of oral therapy for diarrhea: comparison of US practices with American Academy of Pediatrics recommendations. *Pediatrics* 1991;87:28–33.
87. Wendland BE, Arbus GS. Oral fluid therapy: sodium and potassium content and osmolality of some commercial “clear” soups, juices and beverages. *Canadian Medical Association Journal* 1979;121:564–6.
88. Duggan C, Fontaine O, Pierce NF, *et al.* Scientific rationale for a change in the composition of oral rehydration solution. *JAMA: the Journal of the American Medical Association* 2004;291:2628–31.
89. Hahn S, Kim Y, Garner P. Reduced osmolality oral rehydration solution for treating dehydration caused by acute diarrhoea in children. *Cochrane Database of Systematic Reviews* 2007;(4):CD002847.
90. Gavin N, Merrick N, Davidson B. Efficacy of glucose-based oral rehydration therapy. *Pediatrics* 1996;98:45–51.
91. Fontaine O, Gore SM, Pierce NF. Rice-based oral rehydration solution for treating diarrhoea. *Cochrane Database of Systematic Reviews* 2000;(2):CD001264. Update in *Cochrane Database of Systematic Reviews* 1998;(4):CD001264.
92. CHOICE Study Group. Multicenter, randomized, double-blind clinical trial to evaluate the efficacy and safety of a reduced osmolality oral rehydration salts solution in children with acute watery diarrhea. *Pediatrics* 2001;107:613–18.
93. Sack DA, Islam S, Brown KH. Oral therapy in children with cholera: a comparison of sucrose and glucose electrolyte solutions. *Journal of Pediatrics* 1980;96:20–5.
94. Santosham M. Glycine-based oral rehydration solution: reassessment of safety and efficacy. *Journal of Pediatrics* 1986;109:795–801.
95. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957;19:823–32.
96. National Patient Safety Agency. *Reducing the Harm Caused By Misplaced Naso and Orogastric Feeding Tubes in Babies under the Care of Neonatal Units*. NPSA Safety Alert No. 9. London: National Patient Safety Agency; 2005.
97. Mackway-Jones K, editor. *Advanced Paediatric Life Support: The Practical Approach*. 4th ed. London: BMJ Books/Blackwells; 2005.
98. Alam AN, Sarker SA, Molla AM, *et al.* Hydrolysed wheat based oral rehydration solution for acute diarrhoea. *Archives of Disease in Childhood* 1987;62:440–4.
99. Bhargava SK, Sachdev HP, Das GB, *et al.* Oral rehydration of neonates and young infants with dehydrating diarrhea: comparison of low and standard sodium content in oral rehydration solutions. *Journal of Pediatric Gastroenterology and Nutrition* 1984;3:500–5.
100. Patra FC, Mahalanabis D, Jalan KN, *et al.* Can acetate replace bicarbonate in oral rehydration solution for infantile diarrhoea? *Archives of Disease in Childhood* 1982;57:625–7.
101. Maulen-Radovan I, Gutierrez-Castrellón P, Hashem M, Neylan M, Baggs G, Zaldo R, *et al.* Safety and efficacy of a premixed, rice-based oral rehydration solution. *Journal of Pediatric Gastroenterology and Nutrition* 2004;38:159–63.
102. Neville KA, Verge CF, Rosenberg AR, *et al.* Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomised study. *Archives of Disease in Childhood* 2006;91:226–32.
103. Phin SJ, McCaskill ME, Browne GJ, *et al.* Clinical pathway using rapid rehydration for children with gastroenteritis. *Journal of Paediatrics and Child Health* 2003;39:343–8.
104. Reid SR, Bonadio WA. Outpatient rapid intravenous rehydration to correct dehydration and resolve vomiting in children with acute gastroenteritis. *Annals of Emergency Medicine* 1996;28:318–23.
105. Moineau G, Newman J. Rapid intravenous rehydration in the pediatric emergency department. *Pediatric Emergency Care* 1990;6:186–8.
106. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Critical Care Medicine* 2002;30:1365–78.
107. Anonymous. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. *British Medical Journal* 1998;317:235–40.

108. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Annals of Internal Medicine* 2001;135:149–64.
109. Petros A, Schindler M, Pierce C, *et al.* Human albumin administration in critically ill patients. Evidence needs to be shown in paediatrics. *British Medical Journal* 1998;317:882.
110. National Patient Safety Agency. *Reducing the Risk of Hyponatraemia When Administering Intravenous Infusions to Children*. NPSA/2007/22. London: NPSA; 2007.
111. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: A case for using isotonic saline. *Pediatrics* 2003;111:227–30.
112. Coulthard MG. Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? *Archives of Disease in Childhood* 2008;93:335–40.
113. Skellett S, Mayer A, Durward A, *et al.* Chasing the base deficit: Hyperchloraemic acidosis following 0.9% saline fluid resuscitation. *Archives of Disease in Childhood* 2000;83:514–16.
114. Holliday MA, Friedman AL, Wassner SJ. Extracellular fluid restoration in dehydration: a critique of rapid versus slow. *Pediatric Nephrology* 1999;13:292–7.
115. Weaver L. Anatomy and embryology. In: Walker WA, Durie PR, Hamilton RJ, Walker-Smith JA, Watkins JB, editors. *Pediatric Gastrointestinal Disease*. 2nd ed. St Louis: Mosby; 1996.
116. Johnson JE, Sullivan PB. The management of acute diarrhoea. *Current Paediatrics* 2003;13:95–100.
117. Khin MU, Nyunt NW, Myo K, *et al.* Effect on clinical outcome of breast feeding during acute diarrhoea. *British Medical Journal* 1985;290:587–9.
118. Sandhu BK, Isolauri E, Walker-Smith JA, *et al.* A multicentre study on behalf of the European Society of Paediatric Gastroenterology and Nutrition Working Group on Acute Diarrhoea. Early feeding in childhood gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 1997;24:522–7.
119. Brown KH, Gastanaduy AS, Saavedra JM, *et al.* Effect of continued oral feeding on clinical and nutritional outcomes of acute diarrhea in children. *Journal of Pediatrics* 1988;112:191–200.
120. Shaikh S, Molla AM, Islam A, *et al.* A traditional diet as part of oral rehydration therapy in severe acute diarrhoea in young children. *Journal of Diarrhoeal Diseases Research* 1991;9:258–63.
121. Nanulescu M, Condor M, Popa M, *et al.* Early re-feeding in the management of acute diarrhoea in infants of 0–1 year of age. *Acta Paediatrica, International Journal of Paediatrics* 1995;84:1002–6.
122. Chew F, Penna FJ, Peret Filho LA, *et al.* Is dilution of cows' milk formula necessary for dietary management of acute diarrhoea in infants aged less than 6 months? *Lancet* 1993;341: 194–7.
123. Fox R, Leen CL, Dunbar EM, *et al.* Acute gastroenteritis in infants under 6 months old. *Archives of Disease in Childhood* 1990;65:936–8.
124. Ransome OJ, Roode H. Early introduction of milk feeds in acute infantile gastro-enteritis. A controlled study. *South African Medical Journal* 1984;65:127–8.
125. Conway SP, Ireson A. Acute gastroenteritis in well nourished infants: comparison of four feeding regimens. *Archives of Disease in Childhood* 1989;64:87–91.
126. Valois S, Costa-Ribeiro H Jr, Mattos A, *et al.* Controlled, double-blind, randomized clinical trial to evaluate the impact of fruit juice consumption on the evolution of infants with acute diarrhea. *Nutrition Journal* 2005;4:23.
127. Jan A, Rafi M, Mustafa S, *et al.* Evaluation of dowdo (wheat-milk gruel) in children with acute diarrhoea. *JPMA – Journal of the Pakistan Medical Association* 1997;47:12–16.
128. Alarcon P, Montoya R, Rivera J, *et al.* Effect of inclusion of beans in a mixed diet for the treatment of Peruvian children with acute watery diarrhea. *Pediatrics* 1992;90:58–65.
129. Mitra AK, Rahman MM, Mahalanabis D, *et al.* Evaluation of an energy-dense meal liquefied with amylase of germinated wheat in children with acute watery diarrhoea: A randomized controlled clinical trial. *Nutrition Research* 1995;15:939–51.
130. Darling JC, Kitundu JA, Kingamkono RR, *et al.* Improved energy intakes using amylase-digested weaning foods in Tanzanian children with acute diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 1995;21:73–81.
131. Alarcon P, Montoya R, Perez F, *et al.* Clinical trial of home available, mixed diets versus a lactose-free, soy-protein formula for the dietary management of acute childhood diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 1991;12:224–32.
132. Grange AO, Santosham M, Ayodele AK, *et al.* Evaluation of a maize-cowpea-palm oil diet for the dietary management of Nigerian children with acute, watery diarrhea. *Acta Paediatrica* 1994;83:825–32.
133. Maulen-Radovan I, Brown KH, Acosta MA, *et al.* Comparison of a rice-based, mixed diet versus a lactose-free, soy-protein isolate formula for young children with acute diarrhea. *Journal of Pediatrics* 1994;125:699–706.
134. Simakachorn N, Tongpenyai Y, Tongtan O, *et al.* Randomized, double-blind clinical trial of a lactose-free and a lactose-containing formula in dietary management of acute childhood diarrhea. *Journal of the Medical Association of Thailand* 2004;87:641–9.
135. Gabr M, Maraghi S, Morsi S. Management of lactose intolerance secondary to acute diarrhea with a soy-based, lactose-free formula. *Clinical Therapeutics* 1979;2:271–6.
136. Finkelstein JA, Schwartz JS, Torrey S. Common clinical features as predictors of bacterial diarrhea in infants. *American Journal of Emergency Medicine* 1989;7:469–73.
137. Santosham M, Goepf J, Burns B, *et al.* Role of a soy-based lactose-free formula in the outpatient management of diarrhea. *Pediatrics* 1991;87:619–22.
138. Bhan MK, Arora NK, Khoshoo V, *et al.* Comparison of a lactose-free cereal-based formula and cow's milk in infants and children with acute gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 1988;7:208–13.
139. Romer H, Guerra M, Pina JM, *et al.* Realimentation of dehydrated children with acute diarrhea: comparison of cow's milk to a chicken-based formula. *Journal of Pediatric Gastroenterology and Nutrition* 1991;13:46–51.
140. Casburn-Jones AC, Farthing MJG. Management of infectious diarrhoea. *Gut* 2004;53:296–305.
141. Nelson JD, Kusmiesz H, Jackson LH, *et al.* Treatment of Salmonella gastroenteritis with ampicillin, amoxicillin, or placebo. *Pediatrics* 1980;65:1125–30.
142. Chiu CH, Lin TY, Ou JT. A clinical trial comparing oral azithromycin, cefixime and no antibiotics in the treatment of acute uncomplicated Salmonella enteritis in children. *Journal of Paediatrics and Child Health* 1999;35:372–4.
143. Kazemi M, Gumpert TG, Marks MI. A controlled trial comparing sulfametboxazole-trimethoprim, ampicillin, and no therapy in the treatment of salmonella gastroenteritis in children. *Journal of Pediatrics* 1973;83:646–50.
144. Garcia de OD, Trujillo H, Agudelo N, *et al.* Treatment of diarrhea in malnourished infants and children. A double-blind study comparing ampicillin and placebo. *American Journal of Diseases of Children* 1974;127:379–88.

145. Robins-Browne RM, Mackenjee MK, Bodasing MN, et al. Treatment of Campylobacter-associated enteritis with erythromycin. *American Journal of Diseases of Children* 1983;137:282–5.
146. Pai CH, Gillis F, Tuomanen E, et al. Erythromycin in treatment of Campylobacter enteritis in children. *American Journal of Diseases of Children* 1983;137:286–8.
147. Salazar-Lindo E, Sack RB, Chea-Woo E, et al. Early treatment with erythromycin of *Campylobacter jejuni*-associated dysentery in children. *Journal of Pediatrics* 1986;109:355–60.
148. Pai CH, Gillis F, Tuomanen E, et al. Placebo-controlled double-blind evaluation of trimethoprim-sulfamethoxazole treatment of *Yersinia enterocolitica* gastroenteritis. *Journal of Pediatrics* 1984;104:308–11.
149. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet* 2002;360:1375–80.
150. Abdel-Maboud AI, Rossignol JF, el-Kady MS, et al. Cryptosporidiosis in Benha, study of some recent modalities in diagnosis and treatment. *Journal of the Egyptian Society of Parasitology* 2000;30:717–25.
151. Wolfsdorf J, Myer EC. Trimethoprim-sulphonamide mixture in the treatment of infantile gastro-enteritis. *South African Medical Journal* 1973;47:1887–9.
152. Robins-Browne RM, Coovadia HM, Bodasing MN, et al. Treatment of acute nonspecific gastroenteritis of infants and young children with erythromycin. *American Journal of Tropical Medicine and Hygiene* 1983;32:886–90.
153. Oberhelman RA, Javier de la CF, Vasquez GE, et al. Efficacy of trimethoprim-sulfamethoxazole in treatment of acute diarrhea in a Mexican pediatric population. *Journal of Pediatrics* 1987;110:960–5.
154. Rodriguez RS, Chavez AZ, Galindo E. A randomized, controlled, single-blind study comparing furazolidone with trimethoprim-sulfamethoxazole in the empirical treatment of acute invasive diarrhea. *Scandinavian Journal of Gastroenterology – Supplement* 1989;169:47–53.
155. De Bruyn G, Hahn S, Borwick A. Antibiotic treatment for travellers' diarrhoea. *Cochrane Database of Systematic Reviews* 2000;(3):CD002242.
156. Wong CS, Jelacic S, Habeeb RL, et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *New England Journal of Medicine* 2000;342:1930–6.
157. Bell BP, Griffin PM, Lozano P, et al. Predictors of hemolytic uremic syndrome in children during a large outbreak of *Escherichia coli* O157:H7 infections. *Pediatrics* 1997;100:E12.
158. Lee WS, Puthuchery SD, Boey CC. Non-typhoid Salmonella gastroenteritis. *Journal of Paediatrics and Child Health* 1998;34:387–90.
159. Nelson EA, Mok TC, Yu LM. Retrospective comparison of management of gastro-enteritis in hospitalised children. *Annals of Tropical Paediatrics* 2002;22:165–71.
160. Roslund G, Hepps TS, McQuillen KK. The role of oral ondansetron in children with vomiting as a result of acute gastritis/gastroenteritis who have failed oral rehydration therapy: a randomized controlled trial. *Annals of Emergency Medicine* 2008;52:22–9.
161. Stork CM, Brown KM, Reilly TH, et al. Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. *Academic Emergency Medicine* 2006;13:1027–33.
162. Joint Formulary Committee. *British National Formulary*. 54 ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2007.
163. Freedman SB, Adler M, Seshadri R, et al. Oral ondansetron for gastroenteritis in a pediatric emergency department. *New England Journal of Medicine* 2006;354:1698–705.
164. Ramsook C, Sahagun-Carreón I, Kozinetz CA, et al. A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. *Annals of Emergency Medicine* 2002;39:397–403.
165. Cubeddu LX, Trujillo LM, Talmaciu I, et al. Antiemetic activity of ondansetron in acute gastroenteritis. *Alimentary Pharmacology and Therapeutics* 1997;11:185–91.
166. Watkinson M. A lack of therapeutic response to kaolin in acute childhood diarrhoea treated with glucose electrolyte solution. *Journal of Tropical Pediatrics* 1982;28:306–7.
167. Sebodo T, Iman S, Sobiran H, et al. Carbo-adsorbent (Norit) in the treatment of children with diarrhoea. *Southeast Asian Journal of Tropical Medicine and Public Health* 1982;13:424–6.
168. Szajewska H, Dziechciarz P, Mrukowicz J. Meta-analysis: Smectite in the treatment of acute infectious diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2006;23:217–27.
169. Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, et al. Racecadotril in the treatment of acute watery diarrhea in children. *New England Journal of Medicine* 2000;343:463–7.
170. Cezard JP, Duhamel JF, Meyer M, et al. Efficacy and tolerability of racecadotril in acute diarrhea in children. *Gastroenterology* 2001;120:799–805.
171. Chowdhury HR, Yunus M, Zaman K, et al. The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea. *Acta Paediatrica* 2001;90:605–10.
172. Figueroa-Quintanilla D, Salazar-Lindo E, Sack RB, et al. A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. *New England Journal of Medicine* 1993;328:1653–8.
173. Soriano-Brucher H, Avendano P, O’Ryan M, et al. Bismuth subsalicylate in the treatment of acute diarrhea in children: a clinical study. *Pediatrics* 1991;87:18–27.
174. Li ST, Grossman DC, Cummings P. Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis. *PLoS Medicine* 2007;4:e98.
175. Brooks WA, Santosham M, Roy SK, et al. Efficacy of zinc in young infants with acute watery diarrhea. *American Journal of Clinical Nutrition* 2005;82:605–10.
176. Bahl R, Bhandari N, Saksena M, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. *Journal of Pediatrics* 2002;141:677–82.
177. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation in young children with acute diarrhea in India. *New England Journal of Medicine* 1995;333:839–44.
178. Yalcin SS, Yurdakok K, Tezcan I, et al. Effect of glutamine supplementation on diarrhea, interleukin-8 and secretory immunoglobulin A in children with acute diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 2004;38:494–501.
179. Ashraf H, Rahman MM, Fuchs GJ, et al. Folic acid in the treatment of acute watery diarrhoea in children: a double-blind, randomized, controlled trial. *Acta Paediatrica* 1998;87:1113–15.
180. Lazzarini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2008;(3):CD005436.

181. Al-Sonboli N, Gurgel RQ, Shenkin A, *et al.* Zinc supplementation in Brazilian children with acute diarrhoea. *Annals of Tropical Paediatrics* 2003;23:3–8.
182. Bhatnagar S, Bahl R, Sharma PK, *et al.* Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. *Journal of Pediatric Gastroenterology and Nutrition* 2004;38:34–40.
183. Fischer Walker CL, Bhutta ZA, Bhandari N, *et al.* Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. *Journal of Pediatric Gastroenterology and Nutrition* 2006;43:357–63.
184. Larson CP, Hoque AB, Larson CP, *et al.* Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: A randomized, double-blind, placebo-controlled trial. *Journal of Health, Population and Nutrition* 2005;23:311–19.
185. Sachdev HP, Mittal NK, Mittal SK, *et al.* A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. *Journal of Pediatric Gastroenterology and Nutrition* 1988;7:877–81.
186. Strand TA, Chandyo RK, Bahl R, *et al.* Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. *Pediatrics* 2002;109:898–903.
187. Henning B, Stewart K, Zaman K, *et al.* Lack of therapeutic efficacy of vitamin A for non-cholera, watery diarrhoea in Bangladeshi children. *European Journal of Clinical Nutrition* 1992;46:437–43.
188. Hossain S, Biswas R, Kabir I, *et al.* Single dose vitamin A treatment in acute shigellosis in Bangladesh children: randomised double blind controlled trial. *British Medical Journal* 1998;316:422–6.
189. Yurdakok K, Ozmert E, Yalcin SS, *et al.* Vitamin A supplementation in acute diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 2000;31:234–7.
190. Brown KH, Perez F, Peerson JM, *et al.* Effect of dietary fiber (soy polysaccharide) on the severity, duration, and nutritional outcome of acute, watery diarrhea in children. *Pediatrics* 1993;92:241–7.
191. Vanderhoof JA, Murray ND, Paule CL, *et al.* Use of soy fiber in acute diarrhea in infants and toddlers. *Clinical Pediatrics* 1997;36:135–9.
192. Jacobs J, Jonas WB, Jimenez-Perez M, *et al.* Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Pediatric Infectious Disease Journal* 2003;22:229–34.
193. Jacobs J, Guthrie BL, Montes GA, *et al.* Homeopathic combination remedy in the treatment of acute childhood diarrhea in Honduras. *Journal of Alternative and Complementary Medicine* 2006;12:723–32.
194. Gorbach SL. The discovery of Lactobacillus GG. *Nutrition Today* 1996;31(6 suppl):2–4S.
195. Isolauri E. Probiotics for infectious diarrhoea. *Gut* 2003;52:436–7.
196. Allen SJ, Okoko B, Martinez E, *et al.* Probiotics for treating infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2004;(2):CD003048.
197. Szajewska H. Probiotics and prebiotics in pediatrics: where are we now? *Turkish Journal of Pediatrics* 2007;49:231–44.
198. Szajewska H, Skorka A, Dylag M. Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2007;25:257–64.
199. Henker J, Laass M, Blokhin BM, *et al.* The probiotic *Escherichia coli* strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. *European Journal of Pediatrics* 2007;166:311–18.
200. Sarker SA, Sultana S, Fuchs GJ, *et al.* *Lactobacillus paracasei* strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. *Pediatrics* 2005;116:e221–8.
201. Salazar-Lindo E, Figueroa-Quintanilla D, Cacicano MI, *et al.* Effectiveness and safety of Lactobacillus LB in the treatment of mild acute diarrhea in children. *Journal of Pediatric Gastroenterology and Nutrition* 2007;44:571–6.
202. Department of Health. *National Service Framework for Children, Young People and Maternity Services – Core Standards*. London: Department of Health; 2004.
203. Health Protection Agency. *Guidance on Infection Control In Schools and other Child Care Settings*. London: Health Protection Agency; 2006 [www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947358374].
204. PHLS Advisory Committee on Gastrointestinal Infections. Preventing person-to-person spread following gastrointestinal infections: guidelines for public health physicians and environmental health officers. *Communicable Disease and Public Health* 2004;7:362–84.
205. Nager AL, Wang VJ. Comparison of nasogastric and intravenous methods of rehydration in pediatric patients with acute dehydration. *Pediatrics* 2002;109:566–72.
206. Curtis L. *Unit Costs of Health and Social Care*. Canterbury: Personal and Social Services Research Unit, University of Kent at Canterbury; 2007.
207. Joint Formulary Committee. *British National Formulary*. 55 ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2008.
208. NHS Supply Chain Catalogue 2009 [www.supplychain.nhs.uk/portal/page/portal/Public/NHS-CAT].
209. Paediatric Formulary Committee. *BNF for Children 2007*. London: BMJ Publishing Group, RPS Publishing, and RCPCH Publications; 2007.
210. National Institute for Health and Clinical Excellence. *The Guidelines Manual 2007*. London: NICE; 2007.
211. Boccia G, Buonavolonta R, Coccorullo P, *et al.* Dyspeptic symptoms in children: the result of a constipation-induced cologastric brake? *Clinical Gastroenterology and Hepatology* 2008;6:556–60.
212. Brooks WA, Santosham M, Naheed A, *et al.* Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005;366:999–1004.
213. Szajewska H, Skorka A, Ruszczyński M, *et al.* Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2007;25:871–81.
214. Henker J, Laass MW, Blokhin BM, *et al.* Probiotic *Escherichia coli* Nissle 1917 versus placebo for treating diarrhea of greater than 4 days duration in infants and toddlers. *Pediatric Infectious Disease Journal* 2008;27:494–9.
215. Canani RB, Cirillo P, Terrin G, *et al.* Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *British Medical Journal* 2007;335:340.

Index

Notes

'GDG interpretation of evidence' implies GDG translation from evidence to recommendations.
vs denotes comparison, or differential diagnosis.

- abdominal pain, 25
 - causative infections, 24
- absolute risk, ix
- acid-base status measurements, 52
- acidosis, ix, 48
 - hyperchloraemic, xiv
 - in dehydration diagnosis, 50
 - metabolic, 71
 - in shock, 52
- activated charcoal, 109, 110
 - evidence overview, 110
 - evidence summary, 110
- acute phase-proteins, ix
- adenovirus infection. *see* enteric adenovirus infection
- adsorbent agents, 109, 110
 - GDG interpretation of evidence, 116
 - see also* kaolin; smectite
- advice for parents/carers. *see* information/advice for parents/carers
- Aeromonas*, community and GP practice incidence, 30
- aetiological agents
 - bacterial vs viral, diagnosis
 - ESR and CRP, 35
 - IL-6, IL-8 or CRP, 35
 - leucocyte counts, 36
 - quick-read CRP, 35
 - clinical features associated, 24
 - incidence in community and GP practice cases, 30
 - laboratory reports, frequency by year/age, 31
 - see also* clinical diagnosis; *specific pathogens*
- age
 - dehydration risk, 38, 39
 - laboratory reports of aetiological agents, frequency by, 31
- allocation concealment, xi
- alternative/complementary therapies, 125
 - evidence overview, 125
 - evidence summary, 126
 - GDG interpretation of evidence, 126
- American Academy of Pediatrics, IV fluid administration rate, 72
- American Subcommittee on Acute Gastroenteritis, dehydration classification by severity, 45
- amoebic dysentery, 27
- amoxicillin, *Salmonella* gastroenteritis, 90
- ampicillin
 - Escherichia coli* infections, 95
 - Salmonella* gastroenteritis, 90, 91
 - Shigella* gastroenteritis, 94
- anion gap, measurement, 52
- anthropometric measures, ix
- antibiotic therapy, 90
 - Campylobacter* infection. *see* *Campylobacter* gastroenteritis
 - Escherichia coli* infections, 95, 102
 - GDG interpretation of evidences, 101
 - indications, 99
 - Escherichia coli* O157 H7, 99, 102
 - evidence summary, 100
 - Salmonella* infections, 36, 100, 102
 - intramuscular vs oral, 91, 94
 - prior to pathogen identification, 96
 - evidence overview, 96
 - evidence summary, 98
 - GDG interpretation, 101
 - protozoal infections responsive to, 102
 - recommendations, 15, 103
 - role in gastroenteritis, 90
 - Salmonella* infection. *see* *Salmonella* gastroenteritis
 - Shigella* gastroenteritis, 94, 102
 - traveller's diarrhoea. *see* traveller's diarrhoea
 - Yersinia enteritis*, 93, 102
- antibiotics, diarrhoea associated, 26, 34, 101
- antidiarrhoeal agents, ix, 109
 - GDG interpretation of evidence, 116
 - recommendations, 15, 117
 - research recommendations, 117
 - see also* adsorbent agents; antimotility agents; antisecretory agents
- anti-emetic agents, ix, 104
 - evidence overview, 104
 - evidence summary, 108
 - GDG interpretation of evidences, 109
 - research recommendations, 18, 109
 - see also* ondansetron
- antimotility agents, ix, 109, 115
 - evidence overview, 115
- antiprotozoal drug therapy, *Cryptosporidium parvum*, 95
 - see also* *Cryptosporidium parvum* infection
- antisecretory agents, ix, 109, 111
 - evidence overview, 111
 - see also* bismuth subsalicylate; racecadotril
- appendicitis, ix
- appraisal of evidence, ix
- area under curve (AROC), ix
- association, definition, ix
- astroviruses, 28
 - community and GP practice incidence, 30
- audit, clinical, x
- azithromycin, *Salmonella* gastroenteritis, 91

- Bacillus*, community and GP practice incidence, 30
- bacterial gastroenteritis
 - clinical features, 24
 - frequency, stool examination, 28
 - leucocyte counts, 36
 - see also *individual bacterial genera*
- best available evidence, ix
- bias, ix
- bicarbonate levels, 49, 51, 52
 - accuracy of dehydration diagnosis, 50, 52
 - loss in diarrhoea, 52
 - ORS, 64
- biochemical abnormalities, in gastroenteritis, 48
 - blood glucose relationship with electrolytes, 49, 52
 - evidence overview, 48
 - evidence summary, 52
 - GDG interpretation of evidences, 52
 - incidence, 48, 50
 - testing recommendations, 53
 - see also *individual abnormalities (e.g. hyponatraemia)*
- bismuth subsalicylate, 109, 113
 - evidence overview, 113
 - evidence summary, 115
 - GDG interpretation of evidence, 116
- blinding (masking), ix
- blood culture, 11, 36, 37
- blood glucose. see glucose, blood
- blood tests, 35, 48
 - baseline measurements before IVT, 72
 - costs, 146
 - evidence overview, 35
 - evidence summary, 36
 - GDG interpretation of evidences, 36
 - recommendations, 11, 37
- blood urea nitrogen (BUN) levels, 50
 - accuracy of dehydration diagnosis, 50
- bolus fluids, ix
- bottle-fed infants
 - dehydration risk increased, 39
 - stools, 21
- breastfeeding/breast-fed infants, 76
 - dehydration risk reduced, 39
 - during acute diarrhoea, effects on outcome, 76
 - during gastroenteritis, 55
 - during rehydration, 76
 - evidence summary, 77
 - GDG interpretation, 77
 - ORS with, 77
 - stools, 21
 - withdrawal during diarrhoea, 77
 - dehydration associated, 38, 54, 77
- calicivirus infection, 28
 - community and GP practice incidence, 30
 - frequency by year and age, 31
- Campylobacter* gastroenteritis
 - antibiotic therapy, 92
 - erythromycin vs placebo, 92
 - evidence overview, 92
 - evidence summary, 93
 - GDG interpretation, 102
 - community and GP practice incidence, 30
 - duration of diarrhoea, 25
 - frequency as traveller's diarrhoea cause, 33
 - frequency by year and age, 31
- Campylobacter jejuni*, 92
 - frequency, stool examination, 28
- capillary refill time (CRT), ix
 - dehydration detection, 41, 42, 44
 - measured by digital device, 42, 44
- care at home, 137
 - after rehydration, recommendations, 16, 138
 - dehydration, recommendations, 16, 138
 - general advice, 16, 138
 - recommendations, 16, 137
- care escalation, 134
 - factors to consider, 134
 - key symptoms/signs indicating need, 134
 - community face-to-face assessment, 15, 136
 - evidence overview, 134
 - GDG interpretation of evidence, 135
 - remote assessment signs, 15, 135, 136
 - safety netting, 135
 - recommendations, 15, 136
- carers, information/advice for. see information/advice for parents/carers
- case report, x
- case series, x
- case study, x
- case-control study, x
- causative agents. see aetiological agents
- cefixime, *Salmonella* gastroenteritis, 91
- Child Health Epidemiology Reference Group, 1
- chloride, ORS, 64
- cholera, 61, 63, 77
- clay minerals, 109
 - see also kaolin; smectite
- clinical audit, x
- clinical diagnosis of gastroenteritis, 21
 - of causes of gastroenteritis
 - clinical features by pathogen, 24
 - diagnostic indicators, 11, 27
 - differential features/causes, 11, 26, 27
 - non-enteric infections, 26
 - non-infective gastrointestinal disorders, 11, 26, 27
 - surgical disorders, 26
 - see also *under* aetiological agents; diarrhoea
 - definitions of diarrhoea/vomiting. see diarrhoea; vomiting
 - duration of diarrhoea/vomiting, 22
 - see also diarrhoea
 - GDG interpretation of evidences, 26
 - natural history. see natural history of gastroenteritis
 - questions to ask, 27
 - recommendations, 11, 22, 27
 - see also diarrhoea; vomiting
- clinical effectiveness, x
- clinical effectiveness evidence, synthesis of, 6
- clinical importance, x
- clinical question, x
- clinical trial, x
- clinician, definition, x
- Clostridium difficile*, 34, 102
 - community and GP practice incidence, 30
 - frequency, stool examination, 28
- Clostridium perfringens*, community and GP practice incidence, 30

- cluster, x
- cluster randomised trial, x
- Cochrane Collaboration, x
- Cochrane Library, x
- Cochrane review, ORT vs IVT, 142, 150
- coeliac disease, xi, 26
- cohort, xi
- cohort study, xi
- colloid fluids, xi
 - crystalloid fluids vs, 71
- community
 - infectious intestinal disease incidence, 29
 - suggested prevalence of unreported infections, 29
 - viral gastroenteritis incidence, 29, 30
- community face-to-face assessment
 - diagnosis by, recommendations, 12, 46
 - recommendations, 15, 136
- complementary therapy. *see* alternative/complementary therapies
- concealment of allocation, xi
- confidence interval (CI), xi
- confounding variables, ix
- confounding variables (confounder), xi
- conscious state changes, 45
- consensus method, xi
- constipation, xi
- consumables, costs, 143
 - IVT, 146
 - ORT, 145
- continuity of care, 135
- control group, xi
- controlled clinical trial (CCT), xii
- cool extremities, dehydration detection, 42
- cost(s)
 - ORT vs IVT, 142
 - see also* cost-effectiveness
- cost-benefit analysis, xii
- cost-effectiveness
 - definition, xii
 - ORT vs IVT in dehydration treatment, 57, 140
 - bottom-up costing method, 143
 - costs, 142
 - discussion, 150
 - IVT costs, 144
 - literature review, 140
 - method, 141
 - model parameters/assumptions, 141
 - Monte Carlo simulation, 151
 - one-way sensitivity analysis, 148
 - ORT costs, 144
 - results, 148
 - 'worst case' sensitivity analysis, 147, 148, 150
 - rapid IVT, 73
- cost-effectiveness analysis, definition, xii
- cost-minimisation approach, IVT vs ORT in dehydration, 57
- cost-utility analysis, xii
- co-trimoxazole, *Cryptosporidium parvum* infection, 96
- cow's milk
 - formula reintroduction after rehydration, 81, 82
 - lactose-free cow's milk vs, after rehydration, 86
 - protein intolerance, 89
 - special formula vs, refeeding after rehydration, 87
 - see also* milk formulae
- C-reactive protein (CRP)
 - bacterial vs viral gastroenteritis, 35
 - diagnostic accuracy, 35
 - evidence summary, 36
 - GDG interpretation of evidence, 36
 - quick-read, bacterial vs viral gastroenteritis, 35
- Crohn's disease, xii, 26
 - indication for investigations, 32
- cross-sectional study, xii
- Cryptosporidium parvum* infection
 - antiprotozoal drug therapy, 95
 - evidence summary, 96
 - GDG interpretation, 102
 - nitazoxanide vs placebo therapy, 95
 - nitazoxanide/co-trimoxazole vs placebo, 96
 - community and GP practice incidence, 30
 - diagnostic tests, 96
 - frequency as cause of traveller's diarrhoea, 33
 - frequency by year and age, 31
- crystalloid fluids, xii
 - colloid fluids vs, 71
- cytotoxin, xii
- decision analysis, xii
- decision tree, xii
 - ORT vs IVT, 141
- decision-analytic model, ORT vs IVT in dehydration treatment, 57, 141
- declaration of interest, xii
- dehydration, xii, xx, 38
 - assessment, 38
 - biochemical disturbances with, 51
 - see also* biochemical abnormalities, in gastroenteritis
 - care at home recommendations, 16, 138
 - classification by severity, 43
 - advantages of new GDG system, 45
 - American Subcommittee on Acute Gastroenteritis, 45
 - as guide for fluid management, 44
 - ESPGHAN, 43
 - evidence summary, 42
 - GDG interpretation of evidence, 44
 - new GDG system, 12, 44, 46
 - WHO, 43
 - clinical assessment, 38
 - clinical detection, 40
 - evidence overview, 41
 - evidence summary, 42
 - GDG interpretation of evidence, 42
 - 'gold standard', 17, 46
 - key recommendations, 9
 - parental observation vs professionals, 41
 - precision, 41
 - recommendations, 12, 46
 - reference standard, 41, 42
 - systematic review, 41
 - training of clinicians, 45
 - clinical features, 12, 17, 40, 41, 46, 47
 - key recommendations, 9
 - signs. *see* dehydration, signs
 - symptoms, history, 41
 - enteric pathogen frequency, 28
 - fluid deficit percentage, 42

- dehydration (*cont.*)
- hypernatraemic. *see* hypernatraemic dehydration
 - laboratory investigations, 48
 - accuracy of diagnosis by, 50
 - biochemical abnormality prevalence, 48
 - evidence overview, 48
 - evidence summary, 52
 - GDG interpretation of evidence, 52
 - incidence of biochemical anomalies, 48
 - recommendations, 13, 53
 - management, 38, 55
 - key recommendations, 10
 - see also* fluid management; oral rehydration therapy (ORT)
 - mild, 44, 45
 - diagnosis, 38
 - mild-moderate, 43
 - moderate, 44, 45
 - prevalence, 24
 - primary prevention, 13, 54
 - see also* fluid management
 - recurrence after rehydration, 54
 - fluid management, 74
 - frequency, 74
 - GDG interpretation of evidence, 74
 - recommendations, 14, 75
 - risk, 74
 - 'red flag' signs, 12, 45, 46, 135
 - key recommendations, 9
 - monitoring, 45
 - risk factors, 38
 - care at home recommendations, 16, 138
 - evidence overview, 38
 - evidence summary, 40
 - GDG interpretation of evidence, 40
 - recommendations, 40
 - withdrawal of breastfeeding, 38, 54, 77
 - severe, 43, 44, 45
 - ORS volume, 65
 - ORT vs IVT, 57
 - see also* oral rehydration therapy (ORT)
 - severity assessment, 40
 - evidence overview, 41, 42
 - evidence summary, 42
 - GDG interpretation of evidence, 44
 - key recommendations, 9
 - recommendations, 12, 46
 - research recommendations, 17, 46
 - signs, 41
 - differentiated from hypovolaemic shock, 45
 - GDG considerations, 44
 - research recommendations, 17, 46
 - summary of, and sensitivity/specificity, 43
 - see also* dehydration, clinical features
 - viral gastroenteritis, 24
- Delphi process, indicators for care escalation, 134
- developed countries, gastroenteritis, 1
- developing countries
- dehydration risk factors, 38
 - gastroenteritis mortality, 1
 - guideline development and, 3
- dexamethasone, 104
- placebo vs, 106, 108
- diagnosis of gastroenteritis, 21
- clinical. *see* clinical diagnosis of gastroenteritis
 - laboratory. *see* laboratory investigations
 - reconsidering during illness, 21
- diagnostic study, xii
- diagnostic test accuracy, levels of evidence, 7
- diarrhoea, 1
- acute-onset, causes, 21
 - antibiotics associated, 26, 34, 101
 - bloody, 24, 25, 27
 - indication for investigations, 32
 - definition, 21
 - used by GDG, 22
 - differential diagnosis, 26
 - duration, 22
 - dietary fibre effect, 124
 - erythromycin therapy in *Campylobacter* gastroenteritis, 93
 - evidence summary, 23
 - GDG interpretation of evidence, 23
 - homeopathy studies, 125
 - probiotics effect, 128, 129, 132
 - recommendations, 11, 23
 - rice-based vs glucose-based ORS, 63
 - specific infections, 24, 25
 - studies, 22, 23
 - viral vs bacterial infections, 24, 25
 - zinc therapy effect, 118
 - frequency, dehydration risk factor, 39
 - non-infective causes, 26
 - persistence, 22, 24
 - indications for investigations, 34
 - probiotic studies, 127
 - risk factors, 24, 25
 - prevention of spread, 138
 - recommendations, 17, 139
 - stool frequency
 - probiotics effect, 128
 - zinc effect, 120
 - traveller's. *see* traveller's diarrhoea
- dietary fibre, 117, 124
- evidence overview, 124
 - evidence summary, 124
 - GDG interpretation of evidence, 124, 125
- Dioralyte®, 64
- dominance, xii
- double-blind study, xiii
- 'doughy skin', 47, 48
- drug-related conditions, diarrhoea/vomiting, 26
- dysentery, xiii
- shigellosis, 102
 - see also* *Shigella* infections
- dystonic reactions, 104
- dysuria, xiii
- economic evaluation, xiii
- effectiveness. *see* clinical effectiveness
- efficacy, xiii
- elective, xiii
- Electrolade®, 64
- electrolytes
- abnormalities. *see* specific abnormalities
 - baseline measurements before IVT, 72
- endemic, definition, xiii

- Entamoeba histolytica*
 frequency as traveller's diarrhoea cause, 33
 frequency by year and age, 31
- enteric adenovirus infection, 28, 29
 clinical features, 24
 community and GP practice incidence, 30
 frequency as cause of traveller's diarrhoea, 33
 frequency by year and age, 31
- enteric infection, xiii
- enteric viruses
 frequency, stool examination, 28
 see also enteric adenovirus infection; rotavirus infection
- epidemiological data, public health authority access, 34
- epidemiology, xiii
- erythrocyte sedimentation rate (ESR), xiii
 diagnostic accuracy, bacterial vs viral gastroenteritis, 35
- erythromycin
Campylobacter gastroenteritis, 92, 93
 prior to pathogen identification, 96
- 'escalation of care', 2
 see also care escalation
- Escherichia coli* infections
 antibiotic therapy, 95, 102
 duration of diarrhoea, 25
 frequency, stool examination, 28
 non-O157, community and GP practice incidence, 30
- Escherichia coli* Nissle 1917, 133
- Escherichia coli* O157
 H7, 27
 antibiotic therapy indications, 99, 102
 evidence summary, 100
 frequency as cause of traveller's diarrhoea, 33
 indications for investigations, 34, 36
 monitoring of children with, 11, 36, 37
 progression, risk factors, 99, 102
- Escherichia coli* O157, community and GP practice incidence, 30
- ESPGHAN, dehydration severity classification, 43
- evidence level, xiii
 diagnostic test accuracy, 7
 intervention studies, 6
- evidence table, xiii
- evidence-based clinical practice, xiii
- exclusion criteria. see selection criteria
- experimental group, xv
- experimental study, xiii
- experimental treatment, xiii
- expert advisors, 3
- external validity, xiii
- eyes, sunken, 44
 dehydration detection, 42
- feeding after rehydration, 78
 diluted feeds, 78
 recommendations, 15, 89
 reintroduction of milk/liquids, 81
 cow's milk formula, 81, 82
 diarrhoea recurrence, 81, 82
 evidence overview, 81
 evidence summary, 83
 fruit juice, 82
 full-strength vs graded feeding regimens, 81, 82
 GDG interpretation of evidence, 88
 reintroduction of solid foods, 83
 evidence overview, 83
 evidence summary, 85
 GDG interpretation of evidence, 88
 local diet comparisons, 83
 porridge (consistencies), 84
 solid foods vs soy formula, 84
 solid foods, 78
 special milk formulas, 86
 cow's milk formula vs special formula, 87
 cow's milk formula vs treated cow's milk formula, 86
 evidence overview, 86
 evidence summary, 88
 GDG interpretation of evidence, 89
 soy formula in early vs late feeding, 87
 soy formula vs lactose-containing formula, 86
 timing (early vs late), 78, 79
 after ORS, 79
 evidence overview, 79
 evidence summary, 81
 formulae, 79
 GDG interpretation of evidence, 88
 solid foods, 79, 80
 weight gain benefit, 79, 80, 81
- feeding during rehydration, 76
 breastfeeding. see breastfeeding/breast-fed infants
 evidence overview, 76
 evidence summary, 77
 GDG interpretation of evidence, 77
 milk formulae and solids, 78
 recommendations, 14, 78
- feeding, advice, 76
- fever, recommendations, 11, 27
- fibre. see dietary fibre
- fluid(s)
 colloids. see colloid fluids
 crystalloid. see crystalloid fluids
- fluid administration
 regimen, 64
 route, 2
 see also intravenous fluid therapy (IVT); oral rehydration therapy (ORT)
- fluid management, 54
 after rehydration, 74
 GDG interpretation of evidence, 74
 recommendations, 14, 75
 dehydration treatment, 55
 ORT vs IVT, 55
 see also oral rehydration therapy (ORT)
- flow pathway, 19
 intravenous. see intravenous fluid therapy (IVT)
- key recommendations, 10
- new GDG system of dehydration classification, 44
- optimal fluids, 60
- oral rehydration. see oral rehydration therapy (ORT)
- primary economic focus, 8
- primary prevention of dehydration, 54
 evidence overview, 54
 evidence summary, 55
 GDG interpretation of evidence, 55
 recommendations, 13, 55
 see also intravenous fluid therapy (IVT); oral rehydration therapy (ORT)

- focused question, x, xiii
- folic acid, 117, 123
 - evidence overview, 123
 - evidence summary, 123
 - GDG interpretation of evidence, 125
- forest plot, xiii
- fruit juices, 60
 - feeding after rehydration, 82
- furazolidone, prior to pathogen identification, 97

- gastric emptying, delayed, 78
- gastroenteritis, xiv, 1
 - age relationship, 24
 - clinical features, specific pathogens, 24
 - developed countries, 1
 - diagnosis. *see* diagnosis of gastroenteritis
 - duration, 2, *see also* diarrhoea, duration
 - global perspective, 1
 - infective organisms, prevalence, 24
 - inpatients, 2
 - mortality. *see* mortality, gastroenteritis
 - sudden onset, 21
 - symptoms, 1
 - UK prevalence/case numbers, 2
 - see also* diarrhoea; vomiting; *specific aspects*
- gastroenteritis management, 1, 2
 - alternative therapies. *see* alternative/complementary therapies
 - antibiotics. *see* antibiotic therapy
 - at home by parents, 21
 - fluids. *see* fluid management
 - inconsistency of advice/therapy, 2
 - therapies, 104
- gastrointestinal disorders, non-infective, 26
- Gastrolyte-R®, 69
- generalisability, xiv
- Giardia lamblia*
 - community and GP practice incidence, 30
 - frequency as traveller's diarrhoea cause, 33
 - frequency by year and age, 31
- glucose, blood
 - electrolyte relationship in diarrhoea, 49, 52
 - routine testing unnecessary, 52
 - see also* hyperglycaemia; hypoglycaemia
- glucose, in ORS, 64
- glutamine, 117, 122
 - evidence overview, 122
 - evidence summary, 123
 - GDG interpretation of evidence, 125
- gold standard, xiv
- grey standard, xiv
- guideline (this, on diarrhoea and vomiting)
 - aims, 3
 - areas outside remit, 4
 - areas within remit, 3
 - background to need, 2
 - development group. *see* Guideline Development Group
 - development methodology, 5
 - diagnostic test accuracy, 7
 - economic evaluation, 6
 - external review, 8
 - forming and grading recommendations, 8
 - health economics, 7
 - levels of evidence, 6, 7
 - literature search strategy, 5
 - synthesis of clinical effectiveness evidence, 6
 - see also* health economics
 - differences from other guidelines, 3
 - intended readership, 4
 - need for, 3
 - recommendations. *see* recommendations
 - research recommendations. *see* research recommendations
 - scope, 1
 - updating, schedule, 8
 - version for parents/carers and public, 4
- Guideline Development Group (GDG)
 - approach to current guideline, 3
 - development of current guideline, 5
 - membership, v, 3, 5
 - declaration of interests, 5
- guidelines
 - definition, xiv
 - other, on gastroenteritis management, 3

- haemolytic uraemic syndrome (HUS), 27, 34, 99
 - risk factors, 99, 102
 - vomiting, 100
- health economics, xiv, 7
 - aim, 7
 - evaluations in guideline, 6
 - importance for recommendation formulation, 7
 - IVT vs ORT in dehydration, 57
 - ondansetron. *see* ondansetron
 - primary focus on alternative fluid management, 8
 - prioritisation, 7
- Health Protection Agency (HPA), 30, 138
- health technology, xiv
- health technology appraisal (HTA), xiv
- healthcare-associated infections, pathogen frequencies, 28
- heart rate increase, 45
- hepatosplenomegaly, xiv
- heterogeneity, definition, xiv
- hierarchy of evidence, xiv
- home care. *see* care at home
- homeopathy combination therapy, placebo vs, studies, 126
- homeopathy, placebo vs, 125, 126
- homogeneity, definition, xiv
- hospitals, costs related to IVT, 146
- hyperchloraemic acidosis, xiv
- hyperglycaemia, xiv
 - incidence, 49, 51
- hyperkalaemia, xiv
- hypernatraemia, xiv, 48
 - blood glucose relationship, 49
 - incidence, 49, 51, 52
 - ORS associated, 61
- hypernatraemic dehydration, 47
 - definition, 47
 - evidence overview, 47
 - evidence summary, 47
 - GDG interpretation of evidence, 48
 - incidence, 49
 - IVT recommendations, 14, 72, 73
 - see also* intravenous fluid therapy (IVT)

- key recommendations, 10
- ORS composition
recommendations, 13, 66
see also oral rehydration salt (ORS) solution
- ORT vs IVT management, 59
evidence overview, 59
evidence summary, 59
GDG interpretation of evidence, 59
recommendations, 13, 60
- recommendations, 13, 48
serum sodium levels, 47
symptoms/signs, 13, 47, 48
- hyperreflexia, xiv
- hypertonicity, xiv
- hypoglycaemia, xiv, 48
blood glucose testing, 52
definition, 49
in dehydration, 49
incidence, 49
- hypokalaemia, incidence, 51
- hyponatraemia, xv, 48
incidence, 49, 51
IVT optimal compositions for, 68
ORS and, 64
- hypovolaemic shock, xv
dehydration signs *vs.*, 45
diagnosis, 38
fluid administration, 52
importance of diagnosis, 44
IVT indication, 66, 67
IVT regimen and optimal fluid composition, 67, 71
see also intravenous fluid therapy (IVT)
- lactic acidosis, 52
- new GDG dehydration classification system, 12, 44, 46
- severe, 45
- signs and symptoms, 44
key recommendations, 9
- I^2 (statistical heterogeneity), xv
- immunocompromised
definition, xv
Salmonella gastroenteritis, antibiotic treatment, 36
- incidence, xv
- inclusion criteria. *see* selection criteria
- in-depth interview, xv
- infants, xv
- inflammatory bowel disease, xv
see also Crohn's disease; ulcerative colitis
- information/advice for parents/carers, 137
care at home, 16, 137
recommendations, 16, 137
see also care at home
- key recommendations, 10
- prevention of spread, 138
recommendations, 17, 139
- inpatients, gastroenteritis, 2
- intention to treat analysis, xv
- interleukin-6 (IL-6), bacterial *vs* viral gastroenteritis, 35
- interleukin-8 (IL-8), bacterial *vs* viral gastroenteritis, 35
- internal validity, xv
- intervention, xv
- intervention (experimental) group, xv
- intestinal obstruction, xv
- intravenous fluid therapy (IVT), xv, 66
administration rate, 69
evidence overview, 69
evidence summary, 70
GDG interpretation of evidence, 71
key recommendations, 10
recommendations, 14, 72
- baseline electrolytes before, 72
- changing to ORT, 73
evidence overview/summary, 73
GDG interpretation of evidence, 74
recommendations, 14, 74
- complications, costs of, 147
- cost-effectiveness, ORT *vs.* *see* cost-effectiveness
- costs, 144
- dehydration (not shock) treatment, 71
- disadvantages, 59
- equipment costs, 146
- failure, 57
- hypernatraemic dehydration
key recommendations, 10
recommendations, 14, 72, 73
- indications, 66, 67
GDG interpretation of evidence, 67
recommendations, 13, 67
- key recommendations, 10
- optimal fluid composition, 67, 71
evidence summary, 68
key recommendations, 10
recommendations, 14, 73
- ORT *vs.* *see under* oral rehydration therapy (ORT)
- potassium supplementation, 72
- rapid replacement protocol (RRP), 68, 69, 72
cost-effectiveness, 73
evidence overview, 69
evidence summary, 70
GDG interpretation of evidence, 71
key recommendations, 10
mild-to-moderate dehydration, 69, 70
moderate dehydration, 69
recommendations, 14, 72
research recommendations, 18, 73
volume and rate, 72
- recommendations, 13, 72
- regimen for shock, 67
evidence overview, 67
evidence summary, 68
GDG interpretation of evidence, 71
recommendations, 13, 72
regimens, 68
research recommendations, 18, 73
- saline, 68
recommendations, 14, 71, 73
- unscheduled, ORS composition studies, 61
- volume required, 69
assessment and recommendation, 71
dehydration without shock, 71
evidence overview, 69
evidence summary, 70
GDG interpretation of evidence, 71
recommendations, 13, 72
- intussusception, xv, 32

- kaolin, 109, 110
 - evidence overview, 110
 - evidence summary, 110
 - GDG interpretation of evidence, 116
- ketones, urinary, accuracy of dehydration diagnosis, 50
- kwashiorkor, xv

- laboratory investigations, 27
 - bacterial vs viral infections
 - ESR and CRP for diagnosis, 35
 - IL-6, IL-8 or CRP to diagnose, 35
 - leucocyte counts, 36
 - quick-read CRP to diagnose, 35
 - blood tests, 35, *see also* blood tests
 - dehydration assessment. *see* dehydration
 - evidence summary, 32
 - frequency of pathogens by year/age, 31
 - indications, 32
 - recommendations, 11, 34
 - key recommendations, 9
 - most common pathogens, 30, *see also* traveller's diarrhoea
 - children with traveller's diarrhoea, 32
 - need for clinical information for, 34
 - non-stool, 34
 - recommendations, 11, 37
 - stool microbiological investigation, 27
 - see also* stool microbiological investigation
- lactase deficiency, transient mucosal, 76, 89
- lactic acidosis, 52
- Lactobacillus*, probiotics
 - evidence overview, 127
 - see also* probiotics
- Lactobacillus acidophilus* LB, 130
 - see also* probiotics
- Lactobacillus paracasei* strain ST11, 130
 - see also* probiotics
- Lactobacillus rhamnosus* GG, 126, 129
 - see also* probiotics
- Lactobacillus rhamnosus* strains 573L/1, 573L/2, 573L/3, 131
- lactose intolerance, transient, 89
- lactose malabsorption, 82
- lactose-free cow's milk, cow's milk vs, feeding after rehydration, 86
- leucocyte counts, bacterial vs non-bacterial gastroenteritis, 36
- leucocytosis, xv
- levels of evidence. *see* evidence level
- likelihood ratio
 - negative, xvi
 - positive, xviii
- Likert scale, xv
- literature review, xv
 - cost-effectiveness of ORT vs IVT, 140
- literature search strategy, 5
- longitudinal study, xv
- loperamide, 109, 115
 - evidence overview, 115
 - evidence summary, 116
 - GDG interpretation of evidence, 117
- low birthweight, dehydration risk factor, 39
- malabsorption, xvi
- malnutrition, 3
- masking (blinding), ix
- matching, xvi
- mean (arithmetic mean), xvi
- mean difference, xvi
- meningitis, 26
- meta-analysis, xvi
- methodological quality, xvi
- methodology, xvi
- metoclopramide, 104
 - placebo vs, 108
- micronutrients, 117
 - GDG interpretation of evidence, 124
- milk formulae
 - during rehydration, GDG interpretation, 78
 - lactose-containing, soy formula vs, 86
 - see also* cow's milk; feeding after rehydration
- Monte Carlo simulations, ORT vs IVT costs, 151
- mortality, gastroenteritis, 1
 - developed countries, 1
 - prevention strategies, 1
- mucoprotective agent, xvi
- mucous membranes, dry, dehydration detection, 42
- multicentre study, xvi
- nasogastric tube, ORS administration, 65

- National Patient Safety Agency (NPSA), xvi
 - isotonic solution recommendation, 71
 - IV infusions in hypernatraemic dehydration, 72
 - IVT administration rate, 73
 - safety alert on IV infusions, 71
- natural history of gastroenteritis, 23
 - clinical features by pathogen, 24
 - evidence overview, 24
 - evidence summary, 25
 - GDG translation from evidence to recommendation, 25
 - persistent diarrhoea, risk factors. *see* diarrhoea
- NCC-WCH, staff listing, v
- negative likelihood ratio, xvi
- negative predictive value, xvi
- neutrophil counts, bacterial vs non-bacterial gastroenteritis, 36
- NHS Direct, xvi, 134
 - consultations on gastroenteritis, 2
- NHS trust, xxii
- NICE *Technical Manual*, 5, 7
- nitazoxanide, *Cryptosporidium parvum* infections, 95, 102
- non-enteric infections, 26
- non-experimental study. *see* observational study
- norovirus, 28, 29
 - frequency by year and age, 31
- notification of illness, 34
- number needed to treat (NNT), definition, xvi
- nutritional management, 76
 - key recommendations, 10
 - see also* feeding after rehydration; feeding during rehydration

- objective measure, xvi
- observational study, xvii
- odds, xvii

- odds ratio (OR), xvii
- ondansetron, 104
- health economics, 108, 153
 - costs, 154
 - discussion, 155
 - economic analysis, 153
 - effectiveness measure, 153
 - model probabilities, 153
 - results, 154
 - sensitivity analysis, 154
 - intravenous
 - vs metaclopramide vs placebo, 108
 - vs placebo, 106, 108
 - oral, placebo vs, 105, 106, 108
 - benefits, 108
 - economic advantages, 108
 - effect on hospital readmission, 107
 - effect on need for IVT, 107
 - GDG interpretation, 109
 - meta-analysis, 106
 - research recommendations, 18, 109
 - vomiting cessation, 107, 108
 - oral fluids
 - optimal
 - clear fluids vs ORS, 60
 - evidence overview, 60
 - evidence summary, 60
 - GDG interpretation of evidence, 61
 - rehydration after IVT, 68
 - types and effectiveness, 60
 - oral rehydration salt (ORS) solution, xvii, 54
 - advantages, 55
 - cereal-based, 64
 - composition and variations, 61
 - products available in UK, 64
 - glucose-based vs rice-based, 61, 64
 - Cochrane review, 62
 - diarrhoea duration, 63
 - evidence overview, 61
 - evidence summary, 63
 - glycine-based, 64
 - high-osmolarity/low-sodium vs low-osmolarity/low-sodium, 61
 - evidence overview, 61
 - evidence summary, 63
 - GDG interpretation of evidence, 63
 - systematic review, 62
 - home, dehydration prevention, 54
 - hypernatraemia associated, 61
 - IVT vs
 - all grades/types of dehydration, 56
 - see *also* oral rehydration therapy (ORT)
 - nasogastric tube administration, 17, 66
 - not provided, dehydration associated, 38
 - optimal composition, 60, 61
 - evidence overview, 60
 - evidence summary, 63
 - GDG interpretation of evidence, 63
 - key recommendations, 10
 - recommendations, 13, 66
 - oral glucose electrolyte vs oral sucrose solution, 64
 - organic solutes in, 61
 - osmolarity, 61, 62, 64
 - supplementary, after rehydration, 75
 - WHO, composition, 61, 63, 64
 - reduced osmolarity solution vs, 61
 - oral rehydration therapy (ORT), xvii, 54
 - administration rate, rapid, IV fluid vs, 69
 - costs, 144, 150
 - dehydration risk without, 54
 - duration, 65
 - failure, IVT after, 67
 - home, dehydration prevention, 54
 - isotonic solution recommendation by NPSA, 71
 - IVT comparison, 55
 - Cochrane review, 142
 - cost-effectiveness. see cost-effectiveness recommendations, 13, 60
 - IVT vs (all degrees/types of dehydration), 56
 - cost-effectiveness evidence, 57
 - evidence overview, 56
 - evidence summary, 57
 - failure estimates, 56
 - phlebitis risk with IVT, 56
 - risk of failure to rehydrate, 56, 59
 - IVT vs (developed countries) systematic review, 62
 - IVT vs (hypernatraemic dehydration), 59
 - see *also* hypernatraemic dehydration
 - IVT vs (severe dehydration), 57
 - evidence overview, 57
 - evidence summary, 59
 - GDG interpretation of evidence, 59
 - Indonesian RCT, 58
 - Iran RCT, 57
 - reduced osmolarity ORS vs WHO ORS and, 64
 - IVT, changing from, 73
 - recommendations, 74
 - nasogastric tube administration, 65
 - research recommendations, 17, 66
 - optimal composition/administration, 60
 - clear fluids vs ORS, 60
 - recommendations, 13, 66
 - see *also* oral fluids; oral rehydration salt (ORS) solution
 - prevention of dehydration, 54
 - recommendations, 13, 66
 - regimen, 64
 - evidence overview, 64
 - evidence summary, 65
 - GDG interpretation of evidence, 65
 - GDG worked example, 65
 - recommendations, 13, 66
 - research recommendations, 17, 66
 - timing of feeding after, 79
 - traditional approach, 65
 - volume given, 65
 - by body weight, 65
 - GDG recommendation, 65
 - zinc therapy with, 118
 - osmolality, oral rehydration fluids, 60
 - osmolarity, xvii
 - osmosis, xvii
 - otitis media, acute, 26
 - outcome, xvii
 - P* value, xviii
 - paralytic ileus, xvii, 149, 151
 - parasite, xvii

- parents
 - guideline version available for, 4
 - inclusion in GDG, 3
 - information/advice for. *see* information/advice for parents/carers
 - PCT. *see* primary care trust
 - peer review, xvii
 - pH, blood, ix
 - phenothiazines, 104
 - adverse effects, 104
 - phlebitis, xvii
 - costs, 147, 149, 151
 - risk, IVT vs ORT, 56
 - photophobia, xvii
 - placebo, xi, xvii
 - pneumonia, 26
 - point estimate, xvii
 - positive likelihood ratio, xviii
 - positive predictive value, xviii
 - potassium, in oral rehydration fluids, 60, 64
 - power. *see* statistical power
 - predictive value
 - negative, xvi
 - positive, xviii
 - prevalence, xviii
 - primary care, xviii
 - primary care trust (PCT), xviii
 - primary outcome, xviii
 - probability, xviii
 - cost-effectiveness of ORT vs IVT model, 141
 - probiotics, xviii, 126
 - Escherichia coli* Nissle 1917, 133
 - evidence overview (multicentre RCT), 133
 - evidence summary, 133
 - GDG interpretation of evidences, 133
 - Lactobacillus acidophilus* LB, 130
 - evidence overview, 130
 - evidence summary, 130
 - Lactobacillus and Saccharomyces*, 127
 - effect on diarrhoea duration, 128
 - effect on stool frequency, 128
 - evidence overview, 127
 - evidence summary, 129
 - meta-analysis, placebo vs, 128
 - placebo vs, 127
 - Lactobacillus paracasei* strain ST11, 130
 - evidence overview, 130
 - evidence summary, 131
 - Lactobacillus rhamnosus* GG, 129
 - evidence overview, 129
 - evidence summary, 130
 - rotavirus diarrhoea duration, 129
 - Lactobacillus rhamnosus* strains 573L/1, 573L/2, 573L/3, 131
 - evidence overview, 131
 - evidence summary, 131
 - potential benefits, 2
 - research recommendations, 18, 133
 - Saccharomyces boulardii*, 131
 - evidence overview (systematic review), 131
 - evidence summary, 132
- professionals, inclusion in GDG, 3
 - prognostic factor, xviii
 - prospective study, xviii
 - protocol, xviii
 - protozoal infections
 - diarrhoea, 24
 - therapy, 102
 - see also specific infections*
 - pseudomembranous colitis, 34, 102
 - pyloric stenosis, xviii
 - qualitative research, xviii, xix
 - quality-adjusted life years (QALYs), xix
 - IVT vs ORT in dehydration, 57
 - ORT vs IVT, costs, 148, 151
 - quantitative research, xix
 - quasi-random allocation, xix
 - racecadotril, 2, 109
 - evidence overview (placebo trials), 112
 - evidence summary, 113
 - GDG interpretation of evidence, 116
 - research recommendations, 117
 - random allocation, xix
 - randomisation, xix
 - randomised controlled trials (RCT), xii, xix
 - range of advice for parents, 76
 - 'rapid dehydration' strategies, 2
 - Rapolyte®, 64
 - receiver operating characteristic curve (ROC curve), xix
 - recommendations, xiv, 3
 - by GDG, background to, 3
 - forming and grading, 8
 - formulation, importance of health economics, 7
 - key priorities (recommendations), 9
 - summary, 9
 - antibiotic therapy, 15
 - dehydration/shock assessment, 12
 - diagnosis, 11
 - escalation of care, 15
 - fluid management, 13
 - information/advice, 16
 - nutritional management, 14
 - therapy (antidiarrhoeal), 15
 - red flag symptoms and signs, xix, 12, 46, 135
 - dehydration, 45
 - key recommendations, 9
 - re-feeding syndrome, 95
 - referral, urgent, 135
 - regression analysis, xix
 - rehydration
 - care at home recommendations after, 16, 138
 - dehydration recurrence. *see* dehydration
 - feeding after. *see* nutritional management
 - rehydration failure
 - definitions, 58
 - ORT vs IVT, 56
 - relative risk (RR), xix
 - reliability, definition, xx
 - remote assessment, xix, 134
 - challenges, 134
 - diagnosis recommendations, 12, 46
 - escalation of care. *see* care escalation
 - GDG interpretation on signs/symptoms, 135
 - healthcare professionals, 134
 - recommendations for referral, 15, 136
 - urgency and care level considerations, 134

- research recommendations
 antidiarrhoeal agents, 117
 anti-emetic agents, 18, 109
 fluid management, 17, 66
 key priorities, 17
 probiotics, 18, 133
 severity of dehydration, 17, 46
 summary, 19
- respiratory pattern, abnormal, dehydration detection, 42, 44
- retrospective study, xx
- Ringer's lactate, 58, 68
 WHO recommendation, 71
- risk, ix
- risk difference (RD), xx
- risk ratio (RR), xix
- rotavirus infection
 bismuth subsalicylate trial, 113
 clinical features, 24
 community and GP practice incidence, 30
 costs and burden associated, 2
 duration of diarrhoea, 24, 25
 probiotics effect, 129
 frequency, 32
 healthcare-associated infections, 29
 stool examination, 28, 29
 incidence, 2
 Europe, 29
 racecadotril vs placebo, 112
 sequelae after, 24
- Royal Colleges, xx
- Saccharomyces boulardii*, 131
- Saccharomyces* probiotics
 evidence overview, 127
 see also probiotics
- safety netting, xx, 135
 recommendations, 15, 136
- Salmonella* gastroenteritis
 antibiotic therapy, 36, 90
 ampicillin vs placebo, 91
 ampicillin/amoxicillin vs placebo, 90
 antibiotics vs placebo, 90
 azithromycin/cefixime vs placebo, 91
 evidence overview, 90
 evidence summary, 92, 101
 GDG interpretation, 101
 indications, 36, 100
 intramuscular vs oral, 91
 relapses, 91
 trimethoprim/sulfamethoxazole vs placebo, 91
 community and GP practice incidence, 30
 complications, 100
 dehydration, 101
 duration of diarrhoea, 24, 25
 frequency as cause of traveller's diarrhoea, 32, 33
 frequency by year and age, 31
 invasive salmonellosis risk factors, 100, 102
 sequelae after, 24
- salmonellosis, invasive, risk factors, 100, 102
- sample, xx
- Scottish Intercollegiate Guidelines Network (SIGN), xx
- secondary care, xx
- secondary outcome, xx
- selection bias, xx
- selection criteria, xx
- semi-structured interview, xx
- sensitivity, xx
- sensitivity analysis, ondansetron health economics, 154
- septicaemia, indications for investigations, 34
- serum creatinine, accuracy of dehydration diagnosis, 50
- Shigella* infections
 antibiotic therapy, 94, 102
 community and GP practice incidence, 30
 duration of diarrhoea, 25
 frequency as cause of traveller's diarrhoea, 33
 vitamin A therapy vs placebo, 122
- shock, xx
 assessment, 38
 see also hypovolaemic shock
- single-blind study, xx
- skin turgor, xx
 abnormal, in dehydration, 41, 42, 44
 reduced, hypernatraemic dehydration, 48
- small round structured viruses, community and GP practice incidence, 30
- smectite, 110
 evidence overview, 110
 evidence summary, 111
- socio-demographic factors, dehydration risk, 39
- sodium
 in oral rehydration fluids, 60, 64
 serum levels in hypernatraemic dehydration, 47
- sodium chloride solution, NPSA recommendation, 71
- solid feeding. see feeding after rehydration
- soups, 60
- soy formula
 early vs late refeeding after rehydration, 87
 lactose-containing formula vs, after rehydration, 86
 solid foods vs, feeding after rehydration, 84
 with fibre vs without fibre, 124
- soy polysaccharide (fibre), 117
- specificity, xxi
- staff costs, 143
 IVT, 145
 ORT, 145
- stakeholder organisations, vi, 3
- standard deviation (SD), xxi
- standardised mean difference (SMD), xxi
- Staphylococcus aureus*, community and GP practice incidence, 30
- statistical power, xxi
- stool microbiological investigation, 27
 enteric pathogen frequency, 27
 children aged under 2 years study, 28
 community studies vs GP, 29, 30
 evidence overview, 28
 evidence summary, 30
 healthcare-associated infections, 28
 population-based study, 29
 south Wales study, 28
 specific pathogens by year/age, 31
 sub-regional infectious disease hospital study, 28
 surveillance study (1999-2000), 28
 winter surveillance studies, 29
- indications for (GDG), 32
- key recommendations, 9
- recommendations (indications), 11, 34
- sample collection/transport, 11, 34

- structured interview, xxi
- study checklist, xxi
- study population, xxi
- study quality. *see* methodological quality
- study type, xxi
- subject, xxi
- sulfamethoxazole
 - prior to pathogen identification, 97
 - Salmonella* gastroenteritis, 91
 - Yersinia* enteritis, 93
- sulphonamide, prior to pathogen identification, 96
- surgical disorders
 - diarrhoea/vomiting, 26
 - indication for investigations, 32
- survey, xxi
- systematic error, ix
- systematic review, xxi
- systemic, definition, xxi

- tachycardia, xxi, 45
- tachypnoea, xxi
- target population, xxi
- tertiary centre, xxi
- toxic shock syndrome, xxi, 26
- training of clinicians, dehydration/shock
 - detection, 45
- traveller's diarrhoea
 - antibiotic therapy, 98
 - evidence overview, 98
 - evidence summary, 99
 - GDG interpretation, 102
 - evidence summary, 32
 - GDG interpretation of evidence, 32
 - indications for investigations, 34
 - most common pathogens, 32
- trimethoprim
 - prior to pathogen identification, 96, 97
 - Salmonella* gastroenteritis, 91
 - Yersinia* enteritis, 93
- triple-blind study, xxi
- trust (NHS), xxii

- ulcerative colitis, xxii, 26
 - indication for investigations, 32
- undernutrition, dehydration risk factor, 39, 40
- updates (to guideline), schedule, 8
- uraemia, incidence, 49
- urea
 - normal, in dehydration, 51
 - raised levels in dehydration, 52
- urinary tract infection, 26
- urine output
 - accuracy of dehydration diagnosis, 50
 - normal, dehydration detection and, 42
- urine specific gravity, accuracy of dehydration
 - diagnosis, 50

- validity, xxii
- variable, xxii
- Vibrio*, community and GP practice incidence, 30
- viral gastroenteritis
 - clinical features, 24, 25
 - incidence in community, 29, 30
 - suggested prevalence unreported, 30

 - see also* enteric adenovirus infection; rotavirus infection; *other specific viruses*
- vitamin A
 - deficiency, 117
 - GDG interpretation of evidence, 125
- vitamin A supplements, 121
 - evidence overview, 121
 - evidence summary, 122
 - placebo vs, 121
- volume, percentage lost, 41
- vomiting, 1
 - anti-emetic therapy, 104
 - definition, 22
 - used by GDG, 22
 - differential diagnosis, 26
 - duration, 22
 - evidence summary, 23
 - GDG interpretation of evidence, 23
 - recommendation, 11, 23
 - frequency, dehydration risk factor, 39
 - IVT vs ORT in severe dehydration, 58
 - onset, 21
 - predictor of haemolytic uraemic syndrome (HUS), 100
 - prevention of spread, 138
 - recommendations, 17, 139
 - viral gastroenteritis, 24
 - zinc therapy effect, 118, 119

- water, tap, clear fluids vs, dehydration management, 60
- weighted mean difference (WMD), xvi, xxi
- World Health Organization (WHO)
 - dehydration severity classification, 43
 - IVT administration rate, 72, 73
 - see also* intravenous fluid therapy (IVT)
 - oral rehydration solution composition, 61, 63, 64
 - post-rehydration fluid management, 75
 - Ringer's lactate recommendation, 71

- Yersinia* enteritis, antibiotic therapy, 93, 102

- zinc, 117
 - loss/deficiency, 117
- zinc therapy/supplements, 117
 - diarrhoea duration, effect, 118
 - effect on stool frequency, 119
 - evidence overview, 117
 - evidence summary, 120
 - GDG interpretation of evidence, 125
 - multivitamin preparation with, 118
 - ORT with, 118
 - placebo vs, effect on diarrhoea, 119
 - safety//efficacy, 118
 - vomiting, effect on, 118, 121

Other NICE guidelines produced by the National Collaborating Centre for Women's and Children's Health include:

- Antenatal care: routine care for the healthy pregnant woman
- Fertility: assessment and treatment for people with fertility problems
- Caesarean section
- Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people
- Long-acting reversible contraception: the effective and appropriate use of long-acting reversible contraception
- Urinary incontinence: the management of urinary incontinence in women
- Heavy menstrual bleeding
- Feverish illness in children: assessment and initial management in children younger than 5 years
- Urinary tract infection in children: diagnosis, treatment and long-term management
- Intrapartum care: care of healthy women and their babies during childbirth
- Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years
- Surgical management of otitis media with effusion in children
- Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period
- Induction of labour
- Surgical site infection: prevention and treatment of surgical site infection

Guidelines in production include:

- When to suspect child maltreatment
- Hypertensive disorders in pregnancy
- Neonatal jaundice
- Constipation in children
- Bacterial meningitis and meningococcal septicaemia in children
- Pregnant women with complex social factors
- Autism in children and adolescents
- Multiple pregnancy

Enquiries regarding the above guidelines can be addressed to:

National Collaborating Centre for Women's and Children's Health

King's Court
Fourth Floor
2-16 Goodge Street
London
W1T 2QA
enquiries@ncc-wch.org.uk

A version of this guideline for parents, carers and the public is available from the NICE website (www.nice.org.uk/CG84) or from NICE publications on 0845 003 7783; quote reference number N1845.

ISBN 978-1-906985-14-1



Published by the Royal College of
Obstetricians and Gynaecologists.
To purchase further copies and for
a complete list of RCOG Press titles,
visit: www.rcogbookshop.com

