Diarrhoea and vomiting

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

Commissioned by the National Institute for Health and Clinical Excellence

Draft for consultation
October 2008

RCOG Press

Contents

Guideline Development Group membership and acknowledgements

Guideline Development Group

GDG members

Stephen Murphy	GDG Chair, Consultant Paediatric Gastroenterologist
Ed Abrahamson	Consultant in Paediatric Emergency Medicine
Richard Churchill	Associate Professor of Primary Care
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 representative
Julie Marriott	Parent/carer representative
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
Gyanranjan Prasad Sinha	Consultant Paediatrician
Jenny Taylor	Paediatric Nurse Practitioner

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

Monica Lakhanpaul	Clinical Co-Director
Rajesh Khanna	Senior Research Fellow
Shona Burman-Roy	Research Fellow
Ana Palanca	Research Fellow
Angela Kraut	Research Fellow
Sjokvist Garcia-Stewart	Research Fellow
Paul Jacklin	Senior Health Economist
Itrat Iqbal	Health Economist
Danielle Worster	Information Scientist
Rosie Crossley	Work Programme Coordinator

External advisers

George B Haycock	Professor Paediatric Nephrology
Craig Williams	Consultant Microbiologist, Glasgow
Martin Richardson	Consultant Paediatrician, Peterborough

Peer reviewers

Olivier Fontaine	Medical Officer, Child and Adolescent Health and Development, WHO
Gill Brookes	
Kathleen Berry	

Acknowledgements

Additional support was received from:

- Anna Bancsi, Martin Dougherty, Rupert Franklin, Eva Gautam-Aitken 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 (PPIP) 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
Company
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
NCCHTA
NCCHTA
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 Ltd
North Yorkshire and York PCT
Northwick Park and St Mark's Hospitals NHS Trust
Nottingham University Hospitals NHS Trust
PERIGON Healthcare Ltd
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 Childrens NHS Trust
SACAR
Sandwell PCT
Sanofi Pasteur MSD
Sanofi-Aventis
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
The Phoenix Partnership
The Royal Society of Medicine
University College London Hospitals (UCLH) Acute Trust
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Wiltshire PCT
Wirral Hospital Acute Trust
York NHS Foundation Trust

Abbreviations

C. diff	*Clostridium difficile*
CI	Confidence Interval
CRP	C-reactive protein
CRT	Capillary Refill Time
DCRT	Digital Capillary Refill Time
DGH	District General Hospital (non-teaching hospital)
EL	Evidence Level (level of evidence)
ELISA	Enzyme-Linked ImmunoSorbent Assay
ESR	Erythrocyte Sedimentation Rate
ESPGHAN	The European Society for Paediatric Gastroenterology
GDG	Guideline Development Group
GPP	Good Practice Point
HE	Health Economics
HPA	Health Protection Agency
IVT	Intravenous rehydration Therapy
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NHS	National Health Service
NICE	National Institue for Health and Clinical Excellence
NPSA	National Patient Safety Agency
OR	Odds Ratio
ORS	Oral Rehydration Solution
ORT	Oral Rehydration Therapy
PPIP	Patient and Public Involvement Programme
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RR	Relative Risk
SD	Standard Deviation
UK	United Kingdom
USA	United States of America
UTI	Urinary Tract Infection
WHO	World Health Organisation
WMD	Weighted Mean Difference

Glossary of terms

Absolute risk	Measures the probability of an event or outcome occurring (e.g. an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the Absolute Risk Reduction.
Absolute Risk Reduction (ARR)	The ARR is the difference in the risk of an event occurring between two groups of patients in a study – for example if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the old drug treatment then the ARR is 10% - 6% = 4%. Thus by using the new drug instead of the old drug 4% of patients can be prevented from dying. Here the ARR measures the risk reduction associated with a new treatment. See also Absolute risk.
Acidosis	A decrease in blood pH below 7.36
Acute gastroenteritis	The rapid onset of diarrhoea less than 10–14 days previously, with or without nausea, vomiting, fever, or abdominal pain.
Acutephase proteins	Blood markers of an inflammatory response
Acute sector	Hospital-based health services which are provided on an in-patient, day case or out-patient basis.
Acute trust	A trust is an NHS organisation responsible for providing a group of healthcare services. An acute trust provides hospital services (but not mental health hospital services which are provided by a mental health trust).
Allied health professionals	Healthcare professionals, other than doctors and nurses, directly involved in the provision of healthcare. Includes several groups such as physiotherapists, occupational therapists, dieticians, etc. (Formerly known as professions allied to medicine or PAMs.)
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	Describes a drug which provides symptomatic relief from diarrhoea. These include adsorbent agents (kaolin and activated charcoal), antisecretory agents (racecadotril and bismuth subsalicylate), antimotility agents and mucoprotective agents (smectite).
Anti-emetic	Describes a drug that relieves nausea and prevents vomiting.
Antimotility agents	Describes a drug that reduces gastrointestinal movement
Antisecretory agents	Describes a drug that reduces or surpresses gastric secretions.
Appendicitis	Inflammation of the appendix.
Applicability	The extent to which the results of a study or review can be applied to the target population for a clinical guideline.
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.
ARR	See Absolute Risk Reduction.

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 a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see Selection bias, Performance bias, Information bias, Confounding, Publication bias.
Blinding or masking	The practice 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	A test performed on physical examination in which the skin is pressed until blanched by the clinician's finger and the time taken for the skin to retun 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 circulatory insufficiency (e.g. shock) or dehydration.
Case-control study	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	Description 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.
Causal relationship	Describes the relationship between two variables whenever it can be established that one causes the other. For example there is a causal relationship between a treatment and a disease if it can be shown that the treatment changes the course or outcome of the disease. Usually randomised controlled trials are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association between two variables. For example, if it happened that everyone who had eaten a particular food became sick, and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food caused the sickness – unless all other possible causes (e.g. environmental factors) had been ruled out.
CCT	See Controlled clinical trial.
CER	Control Event Rate – see Event rate.
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 to 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 governance	A framework through which NHS organisations are accountable for both continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment, or treatment outcomes, of the target population.
Clinical importance	The importance of a particular guideline recommendation to the clinical management of the target population.
Clinical question	This term is 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 with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.
Clinician	A health care professional providing patient care, e.g. doctor, nurse, physiotherapist.
Cluster	A group of patients, rather than an individual, used as the basic unit for investigation. See also Cluster design, Cluster randomisation.
Cluster design	Cluster designs are those where research subjects are not sampled or selected independently, but in a group. For example a clinical trial where patients in a general practice are allocated to the same intervention; the general practice forming a cluster. See also Cluster, Cluster randomisation.
Cluster randomisation	A study in which groups of individuals (e.g. patients in a GP surgery or on a hospital ward) are randomly allocated to treatment groups. 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, Cluster design.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called randomised controlled trials. 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	The Cochrane Library consists of 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 fails to digest and absorb food, caused by a sensitivity to gluten.
Cohort	A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group 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). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Colloid fluids	Substances that do not dissolve into a true solution and do not pass through a semi-permeable membrane. Colloid solutions tend to stay in the intravascular compartment for longer than crystalloids, and therefore less volume is needed. Colloids also increase colloidal osmotic pressure, draining water out of 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. Type of colloids include dextran and gelatin (e.g. Gelofusine® and Haemaccel®).
Combined modality	Use of different treatments in combination (for example surgery, chemotherapy and radiotherapy used together for cancer patients).
Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. 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.

Confounder or confounding factor	Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. 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 statement	A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.
Considered judgement	The application of the collective knowledge of a guideline development group to a body of evidence, to assess its applicability to the target population and the strength of any recommendation that it would support.
Consistency	The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also Homogeneity.
Constipation	A condition in which passing faeces occurs infrequently, or with difficulty.
Control Event Rate	See Event rate.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study 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 health care 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 health care 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. 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.

Crossover study design	A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.
Cross-sectional study	The observation of 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 a 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.
Data set	A list of required information relating to a specific disease.
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 e.g. if their position or department is funded by a pharmaceutical company.
Dehydration	A state of loss of water from the extracellular fluids or cells.
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.
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.
Dysentry	An infection of the intestinal tract which causes severe 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.
EER	Experimental Event Rate – see Event rate.
Effectiveness	See Clinical effectiveness.
Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care.
Elective	Name for clinical procedures that are regarded as advantageous to the patient but not urgent.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.
Endemic	Applied to diseases that are present in or peculiar to particular localities or populations.
Enteric infection	Invasive infection of the bowel
Epidemiology	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.
Event rate	The proportion of patients in a group for whom a specified health event or outcome is observed. Thus, if out of 100 patients, the event is observed in 27, the event rate is 0.27 or 27%. Control Event Rate (CER) and Experimental Event Rate (EER) are the terms used in control and experimental groups of patients respectively.
Evidence based	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
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 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 Event Rate (EER)	See Event rate.
Experimental study	A research study designed to test if 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. Controlled clinical trial and randomised controlled trial are examples of experimental studies.
Experimental treatment	A treatment or intervention (e.g. a new drug) being studied to see if 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, e.g. in routine clinical practice. May also be referred to as the generalisability of study results to non-study patients or populations.

Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
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. E.g. 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 on a common scale, allowing visual comparison of results and examination of the degree of heterogeneity between studies.
Funnel plot	Funnel plots are simple scatter plots on a graph. They show the treatment effects estimated from separate studies on the horizontal axis against a measure of sample size on the vertical axis. Publication bias may lead to asymmetry in funnel plots.
Gastroenteritis	Inflammation of the stomach and intestine, due to acute infection by viruses or bacteria, which causes diarrhoea and 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.
Good practice point	Recommended good practice based on the expert experience of the guideline development group (and possibly incorporating the expertise of a wider reference group). A guideline development group may produce a 'Good practice point' (rather than an evidence based recommendation) on an important topic when there is a lack of research evidence.
Grade of recommendation	A code (e.g. A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool which 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 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 which studies decisions about the use and distribution of health care 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)	A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost effectiveness of a health technology. NICE health technology appraisals are designed to provide patients, health 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	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well conducted study. Well-conducted randomised controlled trials (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	This means that the results of studies included in a systematic review or meta analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also Consistency.
HTA	See Health Technology Appraisal.
Hyperchloraemic acidosis	A consequence of infusions of large quantities of chloride-containing solutions, such as 0.9% normal saline.
Hyperglycaemia	An excessive level of glucose in the bloodstream.
Hyperkalaemia	A serum potassium concentration greater than 5.5 mmol/l.
Hypernatraemia	An electrolyte disturbance in which the sodium concentration in the plasma exceeds 145 mmol/l.
Hyperreflexia	Overactive or overresponsive reflexes.
Hypertonicity	Exceptionally high muscle tension.
Hypoglycaemia	Deficiency of glucose in the bloodstream.
Hyponatraemia	An electrolyte disturbance in which is sodium concentration in the plasma is too low (below 135 mmol/l).
Hypovolaemic shock	A state of decreased blood volume; more specifically, a decrease in volume of blood plasma. It occurs when the volume of the circulatory system is too depleted to allow adequate circulation to the tissues of the body.
Immunocompromised	A condition which makes patients vulnerable to opportunistic infections due to their immune system not functioning normally.
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. Does not use pre-set questions, but is shaped by a defined set of topics or issues.

Inflammatory bowel disease	A group of chronic intestinal diseases characterised by inflammation of the small or large intestine. The two most common types of inflammatory bowel disease are Crohn's disease and ulceratice colitis.
Information bias	Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of blinding), response errors (e.g. lack of blinding if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).
Inguinal hernia	A hernia which occurs in the lower abdomen.
Intention to treat analysis	An analysis of a clinical trial where patients 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.
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.
Interventional procedure	A procedure used for diagnosis or treatment that involves making a cut or hole in the patient's body, entry into a body cavity or using electromagnetic radiation (including X-rays or lasers). The National Institute for Clinical Excellence (NICE) has the task of producing guidance about whether specific interventional procedures are safe enough and work well enough for routine use.
Intestinal obstruction	A blockage of the intestines which produces symptoms of abdominal pain, vomiting and constipation.
Intravenous therapy (IVT)	The giving of liquid substances, intermittently or continuously, directly into a vein.
Intussusception	A condition in which a part of the intestine prolapses (telescopes) into another immediately adjacent section of the intestine.
Kwashiorkor	Severe protein malnutrition, marked by lethargy, growth restriction, anaemia, oedema, potbelly, skin depigmentation, and hair loss or change in hair colour.
Level of evidence	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.
Leucocytosis	Increased white blood cell count.
Likert scale	A survey method of measuring attitudes that asks respondents to specify their level of agreement to 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 study of the same group of people at more than one point in time. (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.

Meta analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible e.g. 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 & Heterogeneity.
Methodology	The overall approach of a research project, e.g. the study will be a randomised controlled trial, of 200 people, over one year.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Mucoprotective agents	A therapeutic agent to protect the lining of the gut.
Multicentre study	A study where subjects were selected from different locations or populations, e.g. a co-operative study between different hospitals; 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)	Describes the probability of having a negative test result in the diseased population compared with that of a non-diseased population, and corresponds to the ratio of the false negative rate divided by the true negative rate [(1 − sensitivity)/specificity].
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	NHS Direct is 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	See Number Needed to Treat.
NNT	See Number Needed to Treat.
Nominal group technique	A technique used for the purpose of reaching an agreement on a particular issue. It uses a variety of postal and direct contact techniques, with individual judgements being aggregated statistically to derive the group judgement. See also Consensus methods.
Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.
Non-systematic review	See Review.
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 to prevent an event which would otherwise occur. E.g. if the NNT=4, then 4 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. e.g. if the NNH=4, then 4 patients would have to be treated for one bad outcome to occur.

Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.
Observation	Observation is a research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. 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.
Odds ratio	Odds are a way of representing probability, especially familiar for betting. 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. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were 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, Risk ratio.
Off-label prescribing	When a drug or device is prescribed outside its specific indication, to treat a condition or disease for which it is not specifically licensed.
Oral rehydration solution (ORS)	Special fluid formations containing as essential ingredients an organic solute (e.g. 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 contains glucose and sodium chloride in specified concentrations.
Oral rehydration therapy (ORT)	The restitution of water and electrolyte deficits in dehydrated patients using an **oral rehydration solution (ORS)**.
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 which obtains food and shelter from another organism.
Pathogens	Disease producing organisms that can exist in many different places.
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.

Performance bias	Systematic differences in care provided apart from the intervention being evaluated. For example, if study participants know they are in the control group they may be more likely to use other forms of care; people who know they are in the experimental group may experience placebo effects, and care providers may treat patients differently according to what group they are in. Masking (blinding) of both the recipients and providers of care is used to protect against performance bias.
Phlebitis	Inflammation of a vein.
Photophobia	An abnormal intolerance to light.
Pilot study	A small scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full scale study begins.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial 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.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Point estimate	A best single estimate (taken from research data) for the true value of a treatment effect or other measurement. For example, researchers in one clinical trial take their results as their best estimate of the real treatment effect – this is their estimate at their point in time. The precision or accuracy of the estimate is measured by a confidence interval. Another clinical trial of the same treatment will produce a different point estimate of treatment effect.
Positive likelihood ratio (+LR)	Describes the probability of having a positive test result in the diseased population compared with that of a non-diseased population, and corresponds to the ratio of the true positive rate divided by the false positive rate [sensitivity/(1 − specificity)].
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.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.
Primary Care Trust	A Primary Care Trust is 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.
Probability	How likely an event is to occur, e.g. how likely a treatment or intervention will alleviate a symptom.
Probiotics	A live microbial food which has beneficial effects by improving the microbial intestinal balance of the host.

Prognostic factor	Patient or disease characteristics, e.g. age or co-morbidity, which 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. See also Prognostic marker.
Prognostic marker	A prognostic factor used to assign patients to categories for a specified purpose – e.g. for treatment, or as part of a clinical trial, according to the likely progression of the disease. For example, the purpose of randomisation in a clinical trial is to produce similar treatment groups with respect to important prognostic factors. This can often be achieved more efficiently if randomisation takes place within subgroups defined by the most important prognostic factors. Thus if age was very much related to patient outcome then separate randomisation schemes would be used for different age groups. This process is known as stratified random allocation.
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 which 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.
Publication bias	Studies with statistically significant results are more likely to get published than those with non-significant results. Meta-analyses that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a funnel plot.
P value	If a study is done to compare two treatments then the P 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 P-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 P is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the confidence interval.
Pyloric stenosis	Narrowing of the stomach outlet so that food cannot pass easily from it into the duodenum, resulting in feeding problems and vomiting.

Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. 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 zero to one scale). One QALY is equal to one year of life in perfect health, or two 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 which counts people and households.
Quasi experimental study	A study designed to test if a treatment or intervention has an effect on the course or outcome of disease. It differs from a controlled clinical trial and a randomised controlled trial in that: a) the assignment of patients to treatment and comparison groups is not done randomly, or patients are not given equal probabilities of selection, or b) the investigator does not have full control over the allocation and/or timing of the intervention, but nonetheless conducts the study as if it were an experiment, allocating subjects to treatment and comparison groups.
Random allocation/Randomisation	A method that uses the play of chance to assign participants to comparison groups in a research 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.
Randomised controlled trial	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the 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. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Red flag	An important symptom and sign whose presence requires urgent action.
Relative risk	A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared to 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. Relative risk is sometimes used as a synonym for risk ratio.

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 the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym of risk ratio.
Royal Colleges	In the UK medical/nursing world the term royal colleges, as for example in 'The Royal College of…..', refers to organisations which 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.
Sampling	Refers to the way participants are selected for inclusion in a study.
Sampling frame	A list or register of names which is used to recruit participants to a study.
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.
Selection bias	Selection bias has occurred if: 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 of patients 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 that can suddenly affect the haemodynamic equilibrium, usually manifested by failure to perfuse or oxygenate vital organs.
SIGN	See Scottish Intercollegiate Guidelines Network
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 description of tissue hydration.
Specific indication	When a drug or a device has a specific remit to treat a specific condition and is not licensed for use in treating other conditions or diseases.
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	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a P 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 P 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, 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	Methodical, according to plan; not random.
Systematic error	Refers to the various errors or biases inherent in a study. See also Bias.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.
Systemic	Involving the whole body.

Tachycardia	An excessive and rapid heart-rate.
Tachypnoea	Rapid breathing.
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 – e.g. in terms of age, disease state, social background.
Tertiary centre	A major medical centre providing complex treatments which 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, which can be life-threatening if not treated.
Triangulation	Use of three or more different research methods in combination; principally used as a check of validity. The more the different methods produce similar results, the more valid the findings.
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.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also External validity, Internal validity.
Variable	A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.

1
2
3

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 commonest 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 United Kingdom. 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 global perspective gastroenteritis in children is of enormous importance.[1] Worldwide, approximately one 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 the WHO, UNICEF, and a group of independent technical experts - the Child Health Epidemiology Reference Group.[2] Most deaths among children under five 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.

Worldwide, in the 1970's there were almost 5 million childhood deaths 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 less than 5 years of age 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 supplements [4] 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 United States in the 1990s it was estimated that childhood diarrhoea was responsible for 200,000 hospitalisations and 300 deaths in children under five years of age 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 United Kingdom to determine the

incidence of gastroenteritis and of rotavirus gastroenteritis (the commonest responsible pathogen) in children under 5 years of age who received medical treatment in primary care settings, in hospital emergency departments, and as hospital in-patients.[6] Approximately 10% of children under 5 years of age 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 hundred children annually. 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 United States.[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 under 5 years of age 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]

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 a half 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 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 health 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, health visitors or from primary care doctors (general practitioner). Others go directly to a hospital Emergency Department. In one study from the United Kingdom, diarrhoeal illness accounted for 16% of medical presentations to a major Paediatric Accident and Emergency Department.[12]

Although most do not require admission to hospital, many children with gastroenteritis are treated as in-patients 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 a 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 United Kingdom 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 in-patient 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],[17],[18],[19],[20],[21],[22] However, this guideline is unique.

Some guidelines have focussed on specific subgroups of children, such as those presenting to a hospital setting. This guideline is intended to apply to children under 5 years of age 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. The Guideline Development Group (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[23]. 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 advisors 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' [24]. 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 due to gastroenteritis.

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, nurses and any healthcare professional involved in the care or management of children aged 5 years and less 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 under 5'. It can be downloaded from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/CG0XX) or ordered via the NHS Response Line (0870 1555 455) quoting reference number Nxxxx.

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 representatives

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 Guideline Leader, 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.[25]

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 the 3rd Quarter 2008); Cochrane Database of Systematic Reviews (3rd Quarter 2008); and Database of Abstracts of Reviews of Effects (1991 to the 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 August 2008 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 [25, 26, 27, 28, 29, 30, 31, 32] and classified using the established hierarchical system shown in Table 1.1.[32] 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++).

Table 1.1 Levels of evidence for intervention studies[31]

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

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 [25].

Table 1.2 Levels of evidence for studies of the accuracy of diagnostic tests[25]

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 minor or no 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.

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.[33]

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 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 was thought that economic considerations would be particularly important in helping to formulate the recommendations for two clinical questions. 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 modeling.[34] Reviews of the limited relevant published economic literature are presented as part of the appendix detailing the original economic analysis.

The economic focus in this guideline was primarily on alternative treatment options for children with dehydration and a decision-analytic model was developed to compare these two options. 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 Appendix X and Y.

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.

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)

Perform stool microbiological investigations if:

- the child is seriously ill with suspected septicaemia
- there is bloody and/or mucoid diarrhoea
- the child is immunocompromised.

Assess hydration with Table 4.6 in order to:

- classify children as non-dehydrated, clinically dehydrated or shocked
- use red flags as warning signs for increased risk of progression to shock.

Table 4.6 Candidate symptoms and signs available for the comprehensive assessment and classification of dehydration.

	No clinically detectable dehydration	**Clinical dehydration** This category represents a spectrum of increasing dehydration severity. With worsening dehydration clinical manifestations may be expected to become more numerous and severe	**Clinical shock** (a combination of features shown in this column must be present to determine a diagnosis of shock)
	Symptoms (remote and face-to-face assessments)		
Clinical feature of dehydration	Well child	Perceived to be unwell or deteriorating[a]	
	Normal conscious state	Excessive or unaccustomed irritability or lethargy	Depressed conscious state
	Normal level of thirst	Increased thirst	
	Normal urine output[b]	Decreased urine output[b]	
	Normal skin colour	Normal skin colour	Pale or mottled skin
	Warm hands and feet	Warm hands and feet	Cold hands and feet
	Signs (face-to-face assessments only)		
	Normal conscious state	Irritability or lethargy[a]	Depressed conscious state
	Normal skin colour and warm peripheries	Normal skin colour and warm peripheries	Pale or mottled skin and/or cold peripheries
	No sunken eyes	Sunken eyes	
	Moist mucous membranes[c]	Dry mucous membranes[d]	
	Normal fontanelle[c]	Depressed fontanelle[e]	
	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)

Red flags may help identify children at the more severe end of the dehydration spectrum in whom there is an increased risk of progression to shock, and for whom referral to hospital should be considered.

[a] Based on parent/clinician global assessment

[b] The presence of this symptom may help to rule out dehydration, but did not have sufficient diagnostic utility to do so in isolation

[c] Except after a drink

[d] Except mouth breather

[e] Relevant to younger infants, the fontanelle becoming progressively smaller and usually closing by 18 months

Notes on how to use this table:

- Symptoms and signs have been separated since only the former are available for remote (telephone) assessment.
- Symptoms and signs need to be interpreted in the context of the presence of risk factors for dehydration and the social and family circumstances.
- The distinction between 'clinical dehydration' and 'red flag dehydration' is not absolute and requires clinical judgement. If there is doubt, the child should be managed as for the more severe end of the spectrum.

In children with gastroenteritis but without clinical dehydration:

- continue usual fluids, including breast or other milk feeds
- encourage the drinking of plenty of fluids
- offer oral rehydration solution (ORS) as supplemental fluid for those at increased risk of dehydration:
  - children less than 2 years of age, especially those aged less than 6 months
  - infants who were of low birth weight
  - children with more than 5 diarrhoeal stools in the previous 24 hours
  - children with more than 2 vomits in the previous 24 hours
  - children with signs of malnutrition.

In children with clinical dehydration, including hypernatraemic dehydration:

- treat with low osmolarity ORS
- give 50 ml/kg of ORS over 4 hours in addition to maintenance fluids
- administer the fluid frequently and in small amounts
- consider supplementation with their usual fluids (including milk feeds or water, but not fruit juices) if they refuse to take adequate quantities of ORS and do not have red flag symptoms or signs of dehydration
- consider administration of ORS via nasogastric tube if they are unable to drink ORS or vomit persistently
- monitor the response to ORT by regular clinical reassessment.

Use intravenous fluid therapy (IVT) for dehydration:

- if clinical assessment confirms or raises suspicion of shock
- if, despite appropriate ORT, there are signs of deterioration with red flag symptoms or signs of dehydration.

Following rehydration:

- give full-strength milk from the outset
- reintroduce the child's usual solid food
- avoid giving fruit juice until diarrhoea has stopped.

Advise parents and carers:

- in children without clinical dehydration and who 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
- in children without clinical dehydration 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
  - offer ORS as additional supplemental fluid
- in children with clinical dehydration:
  - that rehydration is usually possible with oral rehydration solution (oral rehydration therapy)
  - to make up the ORS according to the instructions on the packaging
  - to give the specified amount of ORS (50 ml/kg for rehydration plus maintenance volume) over a 4 hour period
  - to give this amount of ORS in small but frequent feeds
  - to continue breast feeding in addition to giving the ORS
  - to be concerned if

    - the child refuses to take the ORS or persistently vomits
    - does not appear to be recovering
    - appears to have become less well
  - to seek advice from a specified healthcare professional if they are concerned
- following rehydration :
  - child should be encouraged to drink plenty of their usual fluids including milk feeds if these were stopped
  - to reintroduce the child's usual diet
  - to give a specified volume of ORS (5 to 10 ml/kg) following the passage of large watery stools in children at increased risk of dehydration
- that the usual duration of diarrhoea is 5 to 7 days and in most children it resolves within 2 weeks
- that the usual duration of vomiting is 1 or 2 days and in most children it resolves within 3 days
- to seek advice from a specified healthcare professional if children's symptoms are not resolving as expected.

Advise parents and child carers that:*

- handwashing with soap (liquid where possible) in warm running water and careful drying is the most important factor in the prevention of spread of diarrhoea and vomiting
- handwashing should occur after going to the toilet (children) or changing nappies (parents) and before the preparation, serving or eating of food
- towels used by infected children should not be shared
- children should not attend any childcare facility or school when diarrhoea or vomiting is present
- following any episode of diarrhoea and vomiting, children under 5 years old can return to school or other child care facility 48 hours following the last episode of diarrhoea or vomiting
- children should not swim in swimming pools for 2 weeks following the last episode of diarrhoea.

2.2 Summary of recommendations

Diagnosis

Advise parents that:

- the usual duration of diarrhoea is 5–7 days and in most children will resolve within 2 weeks
- the usual duration of vomiting is 1–2 days and in most children will resolve within 3 days.

When considering a diagnosis of gastroenteritis, look for the following key characteristics:

- a recent change in stool consistency to loose or watery stools
- recent onset of vomiting
- recent contact with an individual with acute diarrhoea
- exposure to known source of enteric infection (water or food borne)
- recent foreign travel.

Consider the following symptoms and signs as possible indicators of diagnoses other than gastroenteritis:

- high fever:
  - age less than 3 months: > 38 °C
  - age more than 3 months: > 39 °C.
- rapid breathing or laboured respirations
- altered conscious level (irritability, drowsiness)
- photophobia, neck stiffness and/or bulging fontanelle (in infants)
- non-blanching (haemorrhagic) rash
- blood and/or mucous in stool
- bilious vomiting (green)
- severe or localised abdominal pain
- abdominal distension or rebound tenderness.

* These recommendations are taken from guidelines commissioned by the Department of Health.[35;36]

Perform stool microbiological investigations if:

- the child is seriously ill with suspected septicaemia
- there is bloody and/or mucoid diarrhoea
- the child is immunocompromised.

Consider performing stool microbiological investigations if:

- there is a history of recent overseas travel
- the diarrhoea has not improved by day seven
- there is uncertainty about the diagnosis of gastroenteritis.

Contact the public health authorities if you suspect a local outbreak of gastroenteritis.

If stool microbiology is to be performed:

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

Perform a blood culture if antibiotic therapy is to be given.

Consider measuring CRP in young infants and in children with immune deficiency presenting with diarrhoea and fever.

Monitor full blood count, platelets, urea and electrolytes in children with *E. coli* 0157:H7 infection.

Assessment of dehydration and shock

Recognise the following as being at increased risk of dehydration:

- children aged less than 2 years of age, with even greater risk for those aged less than 6 months
- infants who were of low birth weight
- children with more than 5 diarrhoeal stools in the previous 24 hours
- children with more than 2 vomits in the previous 24 hours
- children who have not been offered or have not been able to tolerate supplementary fluids prior to presentation
- infants in whom breastfeeding has stopped during the illness
- children with signs of malnutrition

During direct or remote assessment ask whether:

- the child has seemed to the carer to be unwell
- there has been excessive or unaccustomed irritability or lethargy
- the child has seemed unusually thirsty
- there has been a reduction in urine output
- the child's appearance has changed (e.g., sunken eyes)
- the skin colour is normal
- the hands and feet are warm.

Assess hydration with Table 4.6 in order to:

- classify children as non-dehydrated, clinically dehydrated or shocked
- use red flags as warning signs for increased risk of progression to shock.

Table 4.6 Candidate symptoms and signs available for the comprehensive assessment and classification of dehydration.

	No clinically detectable dehydration	Clinical dehydration This category represents a spectrum of increasing dehydration severity. With worsening dehydration clinical manifestations may be expected to become more numerous and severe	Clinical shock (a combination of features shown in this column must be present to determine a diagnosis of shock)
	Symptoms (remote and face-to-face assessments)		
Clinical feature of dehydration	Well child	Perceived to be unwell or deteriorating[a] 🚩	
	Normal conscious state	Excessive or unaccustomed irritability or lethargy 🚩	Depressed conscious state
	Normal level of thirst	Increased thirst	
	Normal urine output[b]	Decreased urine output[b]	
	Normal skin colour	Normal skin colour	Pale or mottled skin
	Warm hands and feet	Warm hands and feet	Cold hands and feet
	Signs (face-to-face assessments only)		
	Normal conscious state	Irritability or lethargy[a] 🚩	Depressed conscious state
	Normal skin colour and warm peripheries	Normal skin colour and warm peripheries	Pale or mottled skin and/or cold peripheries
	No sunken eyes	Sunken eyes 🚩	
	Moist mucous membranes[c]	Dry mucous membranes[d]	
	Normal fontanelle[e]	Depressed fontanelle[e] 🚩	
	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)

🚩 Red flags may help identify children at the more severe end of the dehydration spectrum in whom there is an increased risk of progression to shock, and for whom referral to hospital should be considered.

[a] Based on parent/clinician global assessment

[b] The presence of this symptom may help to rule out dehydration, but did not have sufficient diagnostic utility to do so in isolation

[c] Except after a drink

[d] Except mouth breather

[e] Relevant to younger infants, the fontanelle becoming progressively smaller and usually closing by 18 months

Notes on how to use this table:

- Symptoms and signs have been separated since only the former are available for remote (telephone) assessment.
- Symptoms and signs need to be interpreted in the context of the presence of risk factors for dehydration and the social and family circumstances.
- The distinction between 'clinical dehydration' and 'red flag dehydration' is not absolute and requires clinical judgement. If there is doubt, the child should be managed as for the more severe end of the spectrum.

Suspect hypernatraemic dehydration if any of the following signs are present:

- jittery movements
- hypertonicity
- hyperreflexia
- convulsions
- drowsiness or coma.

Do not routinely perform blood biochemical testing.

Monitor serum sodium, potassium, glucose, venous blood gas, chloride, urea and creatinine concentrations if:

- IVT is required for shock
- there are clinical manifestations suggestive of hypernatraemia or acidosis.

Fluid management

In children with gastroenteritis but without clinical dehydration:

- continue usual fluids, including breast or other milk feeds
- encourage the drinking of plenty of fluids
- offer oral rehydration solution (ORS) as supplemental fluid for those at increased risk of dehydration:
  - children less than 2 years of age, especially those aged less than 6 months
  - infants who were of low birth weight
  - children with more than 5 diarrhoeal stools in the previous 24 hours
  - children with more than 2 vomits in the previous 24 hours
  - children with signs of malnutrition.

Rehydrate children, including those with hypernatraemia, using ORS unless they are in shock.

Use low osmolarity ORS (240–250 mOsm/l) for oral rehydration therapy.

In children with clinical dehydration, including hypernatraemic dehydration:

- treat with low osmolarity ORS
- give 50 ml/kg of ORS over 4 hours in addition to maintenance fluids
- administer the fluid frequently and in small amounts
- consider supplementation with their usual fluids (including milk feeds or water, but not fruit juices) if they refuse to take adequate quantities of ORS and do not have red flag symptoms or signs of dehydration
- consider administration of ORS via nasogastric tube if they are unable to drink ORS or vomit persistently
- monitor the response to ORT by regular clinical reassessment.

Use intravenous fluid therapy (IVT) for dehydration:

- if clinical assessment confirms or raises suspicion of shock
- if, despite appropriate ORT, there are signs of deterioration with red flag symptoms or signs of dehydration.

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

If the child remains shocked:

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

If IVT is required for rehydration of non-shocked children:

- use 0.9% sodium chloride with 5% glucose as the initial infusion fluid
- give 50 ml/kg of intravenous fluid over 24 hours (48 hours in hypernatraemic dehydration) in addition to maintenance fluids
- give an additional bolus of 5–10 ml/kg of 0.9% sodium chloride with 5% glucose for each large watery stool passed
- monitor serum electrolytes
- consider monitoring acid/base status
- change to 0.45% sodium chloride with 5% glucose if hypernatraemia or hyperchloraemic acidosis develop.

During IVT, attempt introduction of ORT and, if tolerated:

- stop IVT and complete rehydration with ORT
- give 5–10 ml/kg of ORS for each large watery stool passed.

Following rehydration children should be encouraged to drink plenty of their usual fluids or feed.

If dehydration recurs ORT should be recommenced.

Following rehydration, in those at increased risk of dehydration, give 5–10 ml/kg of ORS following the passage of each large watery stool. These children include:

- children less than 2 years of age, with even greater risk for those aged less than 6 months
- infants who were of low birth weight
- children with more than 5 diarrhoeal stools in the previous 24 hours
- children with more than 2 vomits in the previous 24 hours.

Nutritional management

During oral rehydration therapy – typically a 4-hour time period:

- continue breast feeding
- other milk feeds should normally be withheld
- consider supplementation with the child's usual fluids (including milk feeds or water, but not fruit juices) if they refuse to take adequate quantities of ORS and do not have red flag symptoms or signs of dehydration
- withhold solid foods

Following rehydration:

- give full-strength milk from the outset
- reintroduce the child's usual solid foods
- avoid giving fruit juice until diarrhoea has stopped

Antibiotic therapy

Do not routinely give antibiotics to children with gastroenteritis.

Give appropriate antibiotic treatment to the following:

- those with suspected septicaemia
- those with extra-intestinal metastatic bacterial infection
- infants under 6 months of age with salmonella gastroenteritis
- malnourished or immune deficient children (including HIV/AIDS) with salmonella gastroenteritis
- those with *Clostridium difficile*-associated pseudomembranous enterocolitis, dysenteric shigellosis, dysenteric amoebiasis, or cholera.

Consider antibiotic therapy for those recently returned from overseas travel.

Other therapies

None

Escalation of care

During remote assessment:

- arrange emergency transfer of those with symptoms suggestive of shock to a secondary care facility
- refer for face-to-face assessment those with:
  - symptoms suggesting an alternative serious condition
  - factors indicating an increased risk of dehydration
  - symptoms suggesting clinical dehydration
  - adverse social or family circumstances
- provide appropriate safety netting arrangement to ensure continuity of care and early recognition of clinical deterioration.

During community face-to-face assessment:

- immediately refer (by emergency transfer) to a secondary care facility all children with symptoms and signs of shock

- using clinical judgement, consider early repeat face-to-face reassessment or referral to a secondary care facility those with:
  - symptoms and signs suggesting an alternative and serious diagnosis
  - dehydration associated with red flag symptoms or signs
  - adverse social or family circumstances
- provide appropriate safety netting arrangement to ensure continuity of care and early recognition of clinical deterioration.

Advice for parents/carers

Advise parents and carers:

- in children without clinical dehydration and who 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
- in children without clinical dehydration 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
  - offer ORS as additional supplemental fluid
- in children with clinical dehydration:
  - that rehydration is usually possible with oral rehydration solution (oral rehydration therapy)
  - to make up the ORS according to the instructions on the packaging
  - to give the specified amount of ORS (50 ml/kg for rehydration plus maintenance volume) over a 4 hour period
  - to give this amount of ORS in small but frequent feeds
  - to continue breast feeding in addition to giving the ORS
  - to be concerned if
    - the child refuses to take the ORS or persistently vomits
    - does not appear to be recovering
    - appears to have become less well
  - to seek advice from a specified healthcare professional if they are concerned
- following rehydration :
  - child should be encouraged to drink plenty of their usual fluids including milk feeds if these were stopped
  - to reintroduce the child's usual diet
  - to give a specified volume of ORS (5 to 10 ml/kg) following the passage of large watery stools in children at increased risk of dehydration
- that the usual duration of diarrhoea is 5 to 7 days and in most children it resolves within 2 weeks
- that the usual duration of vomiting is 1 or 2 days and in most children it resolves within 3 days
- to seek advice from a specified healthcare professional if children's symptoms are not resolving as expected.

Advise parents and child carers that:[*]

- handwashing with soap (liquid where possible) in warm running water and careful drying is the most important factor in the prevention of spread of diarrhoea and vomiting
- handwashing should occur after going to the toilet (children) or changing nappies (parents) and before the preparation, serving or eating of food
- towels used by infected children should not be shared
- children should not attend any childcare facility or school when diarrhoea or vomiting is present
- following any episode of diarrhoea and vomiting, children under 5 years old can return to school or other child care facility 48 hours following the last episode of diarrhoea or vomiting
- children should not swim in swimming pools for 2 weeks following the last episode of diarrhoea.

[*] These recommendations are taken from guidelines commissioned by the Department of Health.[35 36]

2.3 Key priorities for research

Assessment for dehydration and shock (Chapter 4)

Studies and audits should be undertaken to assess the effectiveness and acceptability of the novel clinical hydration assessment scheme and approach to ORT recommended in this guideline.

Why is this important?

Previous practice and guidelines have often implied that it is possible to determine the severity of dehydration with some accuracy based on the detection and evaluation of various clinical manifestations. Following a careful review of published research, the GDG concluded that there was little evidence to support this assumption. Many proposed strategies for evaluating the degree of dehydration were based on subjective and arbitrary criteria. The GDG concluded that a simpler approach to clinical evaluation was both practical and sufficient. It was merely necessary to classify children as being 'without clinical evidence of dehydration', 'clinically dehydrated' or 'shocked'. The only caveat was that a number of specific clinical manifestations ('red flags') might point to a risk of progression to shock. The GDG recommendations for fluids management were then directly linked to this assessment strategy. Those with clinical dehydration should be given ORT in a fixed volume (50 ml/kg over four hours). Regular re-evaluation during the process of ORT would determine whether the child required additional fluid to replace their deficit. Those with shock should receive IVT. The GDG believed that this approach to assessment and fluid management was both rational and safe. It would have the important merit of being simple to implement. However, the GDG recognised this was a novel approach and it would be important to evaluate its effectiveness and acceptability in everyday practice.

Fluid management (Chapter 5)

Studies should be undertaken in those who require IVT for rehydration:

- to compare the effectiveness and safety of 0.9% NaCl with 0.45% NaCl solution
- to determine the optimal duration for rehydration – 'rapid rehydration therapy' (e.g., 1–4 hours) versus the traditional approach of slow intravenous rehydration (e.g., 24 hours).
- to evaluate the a strategy of changing to ORT to complete rehydration after an initial short period of IVT.

Why is this important?

Most children with clinical dehydration should be treated with ORT, but some require IVT, for example because they do not tolerate ORT or because they develop hypovolaemic shock. It is agreed that those with shock should be given intravenous bolus treatment with 0.9% NaCl solution. The optimal choice of intravenous fluid solution for *rehydration* is less certain. It has been suggested that the use of 0.9% NaCl might be associated with a risk of hyperchloraemic acidosis, while 0.45% might increase the risk of hyponatraemia. These fluids should be compared in a randomised controlled trial. Rehydration with ORT is usually carried out rapidly, for example over a period of 4 hours. When children undergo rehydration using IVT it is traditional to replace the fluid deficit more slowly – for example over 24 hours. The consequence is that children remain dehydrated and in hospital for a considerably longer time period. It is important that studies are carried out to compare the effectiveness and safety of 'rapid rehydration' with the slower approach. Finally, it is important to determine whether following an initial short period of IVT it is effective and safe to attempt to complete the rehydration process using ORT. If so this might have advantages such as a shorter period of hospitalisation.

Other therapies (Chapter 8)

A randomised controlled trial should be undertaken to further examine the safety of oral ondansetron for the management of persistent vomiting in children receiving ORT.

Why is this important?

Several randomised controlled trials have now shown that in children with persistent vomiting during ORT 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 that in the placebo groups. In one the number of stools passed during the rehydration phase was significantly greater, while 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 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 recurrence of dehydration or re-admission to hospital. If ondansetron is shown to both effective and safe in a secondary care setting then studies could also be undertaken to evaluate its use in primary care settings.

2.4 Summary of research recommendations

Assessment for dehydration and shock (Chapter 4)

Studies should be undertaken to evaluate the diagnostic accuracy of symptoms and signs in children with varying degrees of dehydration using rehydrated weight as the gold standard.

Studies and audits should be undertaken to assess the effectiveness and acceptability of the novel clinical hydration assessment scheme and approach to ORT recommended in this guideline.

Fluid management (Chapter 5)

Studies should be undertaken to compare the effectiveness and acceptability of nasogastric tube administration of ORS with IVT in those children who do not tolerate ORT.

Studies should be undertaken in those who require IVT for rehydration:

- to compare the effectiveness and safety of 0.9% NaCl with 0.45% NaCl solution
- to determine the optimal duration for rehydration – 'rapid rehydration therapy' (e.g., 1–4 hours) versus the traditional approach of slow intravenous rehydration (e.g., 24 hours).
- to evaluate the a strategy of changing to ORT to complete rehydration after an initial short period of IVT.

Other therapies (Chapter 8)

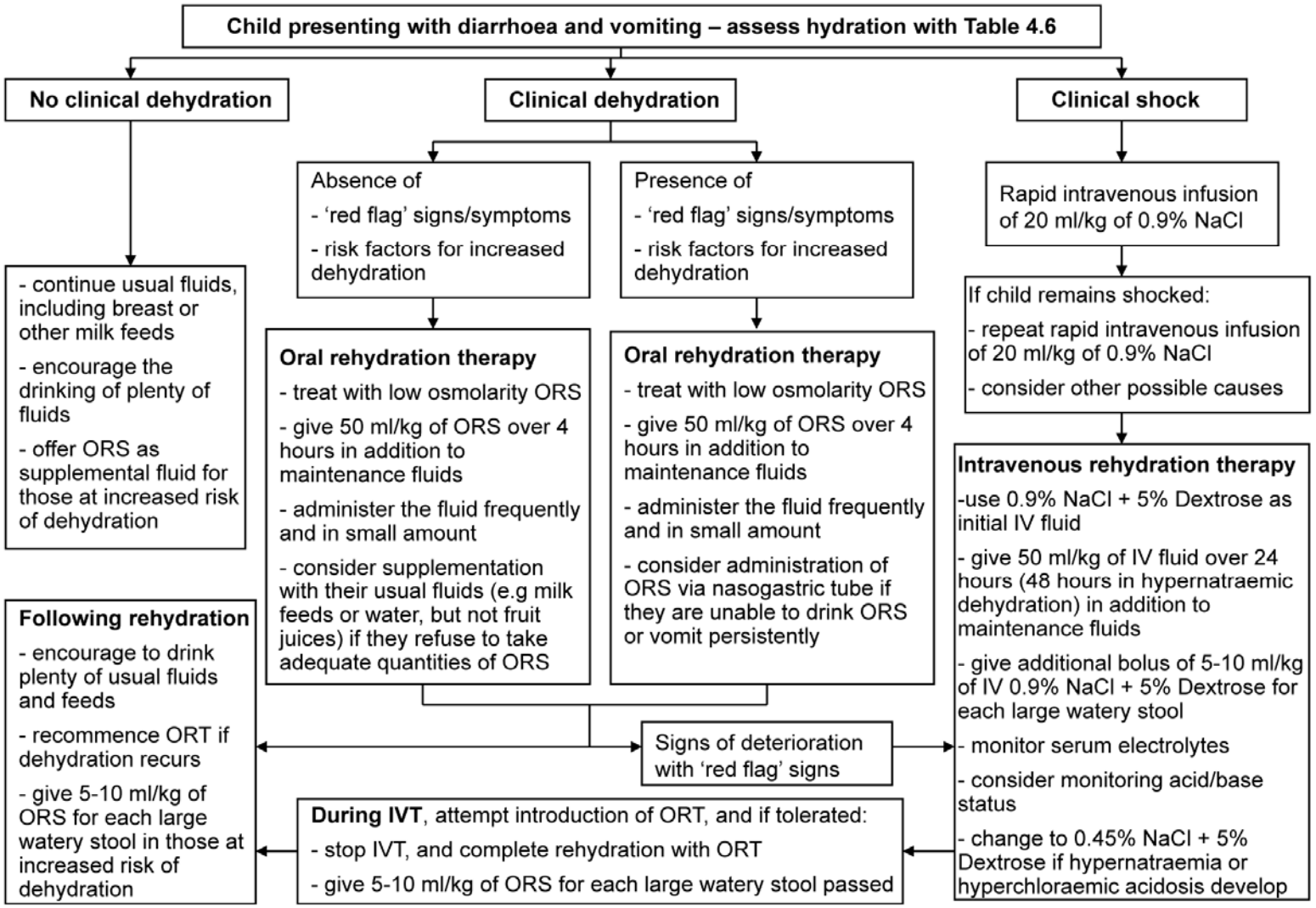
A randomised controlled trial should be undertaken to further examine the safety of oral ondansetron for the management of persistent vomiting in children receiving ORT.

Further studies should be undertaken to examine the effectiveness and safety of racecadotril (an enkephalinase inhibitor), and also smectite (a clay mineral) as antidiarrhoeal agents.

Further randomised controlled trials should be undertaken to further evaluate the effectiveness and safety of specific probiotic agents.

2.5 Flow pathway for fluid management

Flow pathway for fluid management



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' (eg NHS Direct) or through a face-to-face consultations. When children present to a health care 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 eg, 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, breast fed infants may have more frequent and softer stools compared with 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 (e.g. pneumonia), and surgical conditions (e.g. acute appendicitis). In 2007, 7,600 children presented to a paediatric emergency unit in England with suspected acute gastroenteritis.[37] 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 3 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 (ie soft or liquid) and an increase in frequency of bowel movements to 3 or more stools per day have often been used as a definition for epidemiological investigations [38]
- 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 [39]

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. [40]

The GDG considered that the key characteristic of diarrhoea is a 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 recent onset vomiting due to gastroenteritis. 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.'

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

A total of 11 studies were included, six of which provided information on the duration of diarrhoea and five on vomiting.

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 was obtained from the control subjects in four RCTs [41],[42],[43],[44] conducted in Poland, Israel, Colombia and South Africa. Further information was obtained from a cross-sectional study from Kuwait [45], in which almost 50% of the children had bacterial infections. Unfortunately, the data in the Kuwait study was presented without standard deviation values. The primary care based study [46] was a small RCT from Denmark recruiting 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 et al 2005 [41]	Hospital	41	4.0 + 3.0
Gazala E et al 1988 [42]	Hospital	53	3.7 + 1.9

Study	Setting	Sample size	Mean duration of diarrhoea during study period Days (SD)
Lozano JM et al 1994 [43]	Hospital	28	2.3 + 1.7
Haffejee IE et al 1990 [44]	Hospital	120	2.9 + 2.3
Khuffash FA et al 1988 [45]	Hospital	595	7.4 (SD not given)
Rosenfeldt et al 2002 [46]	Community	19	4.8 + 3.5

Data on the duration of vomiting in children was not always clearly or consistently presented in observational studies and hence it was obtained from the control subjects in RCTs. Data on the mean duration of vomiting prior to hospital admission was given in three RCTs: 2.4 days (range 1–6)[47], 1.6 days(SD + 1.2)[48], and 2.5 days (SD + 1.7) [49] respectively. Two very small RCTs provided some data on vomiting during the hospital stay. In one RCT [50], 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 [51] it was reported that of 14 children none experienced any vomiting over four days.

Evidence summary

In 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 regarding the duration of diarrhoea and vomiting in children with gastroenteritis. The available data was 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

Advise parents that:

- the usual duration of diarrhoea is 5–7 days and in most children will resolve within 2 weeks
- the usual duration of vomiting is 1–2 days and in most children will resolve 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 [52],[53],[54],[45], while a case control study [EL = 2+] reported on risk factors for persistent diarrhoea.[55]

Evidence overview

Clinical features associated with infective pathogens
In a prospective cross sectional study from Sweden [52], 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, 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. [EL = 3]

In the second hospital based prospective cross sectional study from Italy [53], the clinical features at presentation were compared in 216 children with viral and bacterial gastroenteritis. Enteric pathogens were detected in 127/216 (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 ($p<0.01$). 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 United Kingdom study [54] included 1148 children less than 16 years of age admitted to a sub-regional infectious disease hospital with a diagnosis of gastroenteritis over a one year period. Of the admitted children 55% (635/1148) were aged less than one year while 5% were more than 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) children were clinically dehydrated with 1% assessed to have greater than 5% dehydration. 79% of children had a history of vomiting before admission and it was more common with rotavirus infection compared to 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 to rotavirus, and abdominal pain was more common in bacterial diarrhoea than diarrhoea of other aetiology ($p<0.001$ for both). 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 [45] the duration of diarrhoea and clinical characteristics associated with various pathogens was 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. The duration of diarrhoea was longer in those with salmonella (mean 12.3 days) when compared to those with other pathogens (Table 3.2). Gastroenteritis with rotavirus infection had a self-limiting course and was associated with few associated manifestations, while salmonella infections had the highest frequency of milk intolerance, malnutrition, and associated features (convulsions, septicaemia). Abdominal pain and bloody diarrhoea were common in infections with shigella, salmonella and campylobacter. Features of extra-intestinal invasions (like toxic look, fever > 3 days, poor feeding, hepatosplenomegaly, and pneumonia) were seen almost exclusively in children with salmonella infections. [EL = 3]

Table 3.2 Duration of diarrhoea in 595 children with gastroenteritis[45]

Clinical Study Group	Number (%)	Mean Duration (days)
Rotavirus	203 (34)	4.8
Salmonellae	98 (17)	12.3
E. coli	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
Overall	595 (100)	7.4

Risk factors for persistent diarrhoea

A case-control study from India [55] investigated possible risk factors for persistent diarrhoea (>14 days). They compared 170 cases with 340 controls (aged 1 – 23 months) who had been admitted to hospital. Cases were children with diarrhoea persisting 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 two 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 1.9–4.5), stool with blood and/or mucus (adjusted OR 2.4; 95%CI 1.3–4.3), indiscriminate use of antibiotics (adjusted OR 2.4; 95%CI 1.6–3.9), stool frequency more than 10 per day (adjusted OR 1.8; 95%CI 1.2–2.8), and persistence of dehydration for more than 24 hours (adjusted OR 1.4; 95%CI 1.2–1.7). [EL = 2+]

Evidence summary

Evidence from four cross-sectional studies [EL = 3] indicates that viral gastroenteritis was associated with a shorter duration of diarrhoea than bacterial gastroenteritis. Vomiting and dehydration were more common with viral gastroenteritis. Bloody diarrhoea and abdominal pain were 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/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 then 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, nevertheless the findings were important, especially given the multi-ethnic composition of the UK population and increasing frequency of overseas travel. Some potentially important risk factors for persistent diarrhoea were identified: persistence of dehydration for > 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.

These findings underline the importance of avoiding unnecessary use of antimicrobials and supporting optimal nutrition in children with gastroenteritis. These matters are considered in details in subsequent chapters.

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, (e.g. sorbitol and xylitol) may occasionally be responsible and on rare occasions certain toxins (e.g. organophosphate insecticides) [56].

Evidence overview

A literature search was undertaken to identify case series (with sample size more than 100) and characteristics of non-gastroenteritis conditions. The list of various alternative diagnoses based upon these case studies and the consensus view of the GDG are given in Table 3.3.

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]
Non- enteric infections:		
• 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.
Non-infective gastrointestinal disorders:		
• ulcerative colitis, Crohn's disease or coeliac disease	Prolonged diarrhoea (> 14 days), bloody diarrhoea	Failure to thrive or weight loss
Surgical disorders:		
• Bowel obstruction, intussusceptions or ischaemic bowel	Bilious vomiting, severe or localised abdominal pain, bloody diarrhoea	Abdominal distension, rebound tenderness, mucoid/bloody stools
Drug-related:		
Review drug history (e.g. antibiotic therapy)		

[a] Children less than 12–18 months of age commonly present with non-specific symptoms and signs of non-enteric infections and non-infective gastrointestinal disorders.

[b] High fever (temperature > 38 °C for age 0–3 months and > 39 °C for age more than 3 months) may occur in gastroenteritis, but may also be a pointer to non-enteric infections.

GDG translation from evidence to recommendation

Based on consensus the GDG identified a number of key points, which they considered were important in the history and examination of the child. 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 (eg urinary tract infection) should be considered.

Recommendations on diagnosis

When considering a diagnosis of gastroenteritis, look for the following key characteristics:

- a recent change in stool consistency to loose or watery stools
- recent onset of vomiting
- recent contact with an individual with acute diarrhoea
- exposure to known source of enteric infection (water or food borne)
- recent foreign travel.

Consider the following symptoms and signs as possible indicators of diagnoses other than gastroenteritis:

- high fever:
  – age less than 3 months: > 38 °C
  – age more than 3 months: > 39 °C.
- rapid breathing or laboured respirations
- altered conscious level (irritability, drowsiness)
- photophobia, neck stiffness and/or bulging fontanelle (in infants)
- non-blanching (haemorrhagic) rash
- blood and/or mucous in stool
- bilious vomiting (green)
- 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, health 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. *E. coli* 0157:H7 is associated with a risk of haemolytic uraemic syndrome – 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 with 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 patients 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 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 [54],[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],[60],[61],[62] gave information on viral pathogens isolated in children with gastroenteritis but they all provided regional data. The last published paper [11] 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 was available for the overall incidence of enteric pathogens in children with gastroenteritis from England and Wales, this information was collected from the website of UK Health Protection Agency (http://www.hpa.org.uk).

A prospective study [54] included 1148 children less than 16 years of age admitted to a sub-regional infectious disease hospital with a diagnosis of gastroenteritis over a one year period (1986–87). The demographic characteristics of the study population have been described in detail under section 3.1. In this study 8.8% (101/1148) children were clinically dehydrated with 1% assessed to have greater than 5% dehydration. Dehydrated children were more likely to have an enteric pathogen identified compared to those without clinical dehydration (61% versus 43%, $p<0.001$). Stool examination identified enteric pathogens in altogether 44.6% 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 cryptosporidia (1.4%) was the commonest protozoal organism detected. [EL = 3]

The second study was a prospective survey [57] recruiting 447 children aged less than two years and admitted to a hospital with gastroenteritis over a one year period (1981–82). 74% of the children were less than 1 year of age and two-thirds of under-1 year old were less than 6 months of age. Pathogenic enteric organisms were isolated in 75% 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% cases (152/447) while all other viruses were detected in 53% 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 study [58] included 215 children admitted to four paediatric units in South Wales with gastroenteritis over a one year period (1987–88). The age of the study population ranged from 2 weeks to 9 years and 61% children were less than one year of age. 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% 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% cases with campylobacter and *E. coli* being the most common. Cryptosporidium spp. was the most common parasite detected. [EL = 3]

A surveillance study [59] reported viral agents isolated from clinical specimens in a regional Public Health Laboratory in 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 calcivirus (0.2%). The prevalence of all the enteric viral agents was reported to be higher in the specimens from the community compared to the specimens from the hospital. 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 (< 16 years) admitted to the hospital with a diagnosis of acute gastroenteritis or who developed the condition following hospitalisation was examined. Gastroenteritis was considered to be health-care associated if symptoms developed ≥ 48 hours following admission. A total of 243 subjects had clinical data and a stool specimen collected, 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% 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 was made of 685 children aged less than 6 years with symptoms of gastroenteritis and included 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 in-patients or attending the A& E department. A viral agent was detected in 366/685 samples (53.4%). A significantly greater number of children from the structured surveillance study group had a viral pathogen detected in their stool specimen compared to 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 to 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, multi-centre study on the incidence of rotavirus in Europe [61], 1010 stool samples were examined from children less than five years of age who presented with gastroenteritis to a regional health service in 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 similar for the two groups of children seen in the emergency department and hospital (60% and 60.7% respectively). In a primary care setting rotavirus was isolated in 32% of the samples. [EL = 3]

The last study was a population-based study [11] undertaken to evaluate the incidence and aetiology of infectious intestinal disease 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. 82% of the participants returned over 22 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 specimen 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 reporting system.

In the community 781 cases were ascertained for infectious intestinal disease with an incidence of 19.4/100 person years (95%CI 18.1 to 20.8) while 8770 people presented to their general practice giving an incidence of 3.3/100 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 6 more cases were present in the community. The ratio was high for cases associated with *E. coli* non-0157, 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 to that of the viruses (rotavirus 35:1). [EL = 3]

Table 3.4 Incidence of infectious intestinal disease identified in patients from community and those presenting to general practice [11]

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/GP cases (95% CI)
Viruses:			
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)
Bacteria			
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)	–
Camplylobacter spp.	8.7 (6.1–12.3)	4.1 (3.3–5.1)	2.1 (1.5–3.0)
Clostridium difficile	1.6 (0.7–3.6)	0.2 (0.1–0.3)	8.0 (3.4–19.3)
Clostridium perfringens	2.4 (1.3–4.7)	1.3 (1.04–1.7)	1.9 (0.97–3.7)
E. coli 0157	0	0.03 (0.01–0.11)	–
E. coli non-0157	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)
Staphylococcus aureus	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)
Protozoa			
Cryptosporidium parvum	0.8 (0.3–2.5)	0.43 (0.3–0.6)	1.9 (0.6–6.1)
Giardia intestinalis	0.5 (0.1–2.2)	0.3 (0.2–0.5)	1.9 (0.5–7.9)
No organism identified	117.3 (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)**

The UK Health Protection Agency 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 sample of children over the last 5 years.

Table 3.5 Laboratory reports of enteric pathogen isolates, England and Wales (2002–2006) stratified by age [63]

Infecting 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 month	24	31	17	11	26	109
1–4 years	22	53	18	15	25	133
						Total: 243
Astrovirus	data unavailable					
Bacillus spp.	data unavailable					
Clostridium botulinum[b]	–	–	–	–	–	–
Calcivirus						
0–1 month	0	0	0	0	0	0
1–11 month	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
Vibrio. cholera	data unavailable					
Cryptosporidium						
0–1 month	7	6	5	10	4	32
1–11 month	75	163	113	156	125	632
1–4 years	839	1516	991	1205	934	5485
						Total: 6149
E. coli O157	data unavailable[c]					
Entamoeba histolytica						
0–1 month	0	0	0	0	0	0
1–11 month	0	0	0	0	0	0
1–4 years	5	4	1	1	2	13
						Total: 13
Giardia lamblia						
0–1 month	30	34	30	23	37	154
1–11 month	333	375	358	283	315	1664
1–4 years	149	168	136	139	120	712
						Total: 2530
Listeria moncytogenes	data unavailable					
Norovirus						
0–1 month	4	6	8	1	2	21
1–11 month	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 (J Med Micro 2005 54: 769–76.)
[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 excludes *S. Typhi amp* and *S. Paratyphi*.

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 hospital settings. The most frequent pathogens causing bacterial gastroenteritis reported in the published studies and HPA website were campylobacter, salmonella and *E. coli*, while cryptosporidium was the most common protozoal infection detected. There was no published population-based data comparing the detection of viral pathogens with bacterial pathogens, however results from the population-based study suggests that cases of non-bacterial gastroenteritis are less likely to be reported to the national surveillance authority compared to 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 was 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 was not available.

Table 3.6 Laboratory reports of enteric pathogens isolates from patients with a history of recent travel abroad (taken from HPA website).[64]

Region of world	Bacterial pathogens				Protozoal pathogens			Viral
	Campylobacter	Salmonella	Shigella	*E. coli* 0157	Cryptosporidium	Giardia	Entamoeba	Enterovirus
Europe	716	1454	14	33	337	52	4	12
Indian sub continent	233	245	176	2	37	92	12	17
North Africa & Middle East	170	265	136	17	27	27	6	1
South East Asia & Far East	132	196	44	–	3	19	5	3
Sub Saharan & southern Africa	58	157	54	4	11	44	27	–
Caribbean	26	111	8	–	11	9	–	–
South & 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**

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 sub-continent and sub-Saharan and southern Africa.

GDG translation from evidence to recommendations

Rotavirus was the predominant single pathogen responsible for gastroenteritis in children. Other viral pathogens, though 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 calcivirus 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.

- If the clinician was in doubt about the diagnosis of gastroenteritis, isolation of a stool pathogen could 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 would also be 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 breast fed 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 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 enterohaemorhagic *Escherichia coli* (mainly *E. coli* 0157:H7) often presents with bloody diarrhoea. These children are at risk of developing haemolytic uraemic syndrome, 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 would also be reasonable to consider investigating children in whom diarrhoea persists for more than 7 days, because certain treatable enteric infections (e.g., 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

Perform stool microbiological investigations if:

- the child is seriously ill with suspected septicaemia
- there is bloody and/or mucoid diarrhoea
- the child is immunocompromised.

Consider performing stool microbiological investigations if:

- there is a history of recent overseas travel
- the diarrhoea has not improved by day seven
- there is uncertainty about the diagnosis of gastroenteritis.

Contact the public health authorities if you suspect a local outbreak of gastroenteritis.

If stool microbiology is to be performed:

- collect, store and transport stool specimens as advised by the investigating laboratory
- provide the laboratory with the 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 under 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 CRP was assessed in all the studies, while ESR and IL-6, 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. It recruited 111 children aged between 1 and 60 months admitted to a hospital with acute diarrhoea lasting more than 12 hours and less than 15 days over a 4 year period. Children with chronic gastrointestinal diseases such as cow's milk protein

intolerance, Crohn's disease, gastroesophageal 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 (31%) had viral gastroenteritis while the remaining 21% had culture-negative infections. The mean CRP level in children with bacterial infections was significantly higher than those with viral infections ($p<0.001$) and culture-negative infections ($p<0.01$). CRP levels were strongly associated with bacterial infections at all the three cut-offs – 12 mg/dl (OR 25.8, 95%CI 7.6–87.9), 20 mg/l (OR 46.4, 95%CI 5.9–365) and 35 mg/l (OR 27, 95%CI 3.4–212.1). The specificity of CRP in detecting bacterial gastroenteritis was high at all the cut-off levels (89% at 12 mg/l and 97% at 20 mg/l and 35 mg/l) but the highest sensitivity was 77% at 12 mg/dl compared to 58% and 44% at the other two cut-off values. The area under ROC curve 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 1.2–9.9) and showed a sensitivity of 42%, specificity of 83% and area under ROC curve 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 if interleukin-6 (IL-6), interleukin-8 (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 compared to those with viral infections ($p<0.001$) and control group ($p<0.001$). IL-8 concentrations were elevated in both bacterial and viral infections and there was statistically no significant difference in the levels between the two groups. Diagnostic accuracy results were analyzed 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 was 83% and 76% while that of IL-6 was 78% and 86%. IL-8 was found to be of less diagnostic value with 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 Quick-Read CRP (QR-CRP) test to detect bacterial gastroenteritis was determined in a convenience sample of 44 children (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 3 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 bedside with a level of 8 mg/l or more considered as a positive test. Stool culture was positive for bacteria in 8 children while rotavirus was isolated in 13 children. The mean CRP concentration was significantly higher in children with bacterial gastroenteritis compared with viral gastroenteritis ($p<0.001$). 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 Israel [68] evaluated the ability of total and differential leucocyte counts in differentiating 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. 192 children had bacterial gastroenteritis (shigella in 130, salmonella and campylobacter in 25 each and *E. coli* in 12) while 46 children were classed as non-bacterial group. The total white blood counts were similar between the etiologic groups but great variation was observed in the differential blood count. The absolute band neutrophil count and the ratio of band neutrophils to total neutrophils was significantly higher in the shigella, salmonella and campylobacter groups compared to the *E. coli* and nonbacterial 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 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, 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) 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, as discussed elsewhere (Chapter 7 on antibiotic therapy), the GDG concluded that few children with bacterial gastroenteritis in the UK required antibiotic treatment. In most children with gastroenteritis diagnostic blood testing was therefore unnecessary. Measurement of CRP might be of value in the minority of children in whom antibiotic therapy would be given if bacterial gastroenteritis was suspected. For example, salmonella gastroenteritis in young infants and in children with an immune deficiency required antibiotics because they were at increased risk of systemic sepsis. Consequently, the GDG agreed that measurement of the CRP should be considered in such cases if they presented with diarrhoea and fever. 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* 0157:H7 infection are at risk of developing haemolytic syndrome and the GDG considered that it would be important to monitor the full blood count, platelets, urea and electrolytes to detect the characteristic changes of microangiopathic haemolytic anaemia, thrombocytopenia and renal insufficiency.

Recommendations on other laboratory investigations in diagnosis

Perform a blood culture if antibiotic therapy is to be given.

Consider measuring CRP in young infants and in children with immune deficiency presenting with diarrhoea and fever.

Monitor full blood count, platelets, urea and electrolytes in children with *E. coli* 0157:H7 infection

4 Assessment for 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. Secondly, the clinician must 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.

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 and 35 papers excluded after going through the hard copies. Finally four case-control studies describing risk factors for the development of dehydration and published in five papers have been included.[69], [70], [71], 40853}, [72] 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 India [69] 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 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 under the age of 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 if the child was severely malnourished with weight for age < 60th 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 under the age of five with acute gastroenteritis (duration not specified) of 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 less 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=0.48) associated with risk of dehydration but the latter association was not statistically significant. Severe under nutrition (weight for age < 60th centile on 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 > 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), withdrawn of fluids during diarrhoea (OR 1.6; 95% CI 1.1 to 2.4, p<0.001) and not giving oral rehydration 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],[73] Cases included children aged less 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 publication [71] reported that though many factors influenced the risk of dehydration, strong association (p<0.001) was seen only for the child's age, birth weight and other anthropometric measures, birth interval and feeding mode. Younger age was significantly associated with an increased risk of dehydration with the risk about 7 times higher in the 2–3 month age group compared to 9–11 months of age. Children of low birth weight (<2500 gms) 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 to those who received breast but no other milk. [EL = 2+]

In the second publication [73], it was reported that breast feeding 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 6–7 times higher risk of developing dehydration compared to children who were exclusively breast fed (adj. OR 6.0, 95%CI 1.8–19.8 for cow's milk and adj. OR 6.9, 95%CI 1.4–33.3 for formula feeds). There was no difference in the risk of dehydration if children continued with their usual feeds during illness (either breast or other feeds), but breast fed children who stopped feeding during illness had a statistically significant increase in the risk (adj. OR 6.4, 95%CI 2.3–17.3). It was also observed that the risk of dehydration was greatest during the time period when breast feeding 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 Bangladesh [72] that included 240 children aged less than two years with acute gastroenteritis (duration < 7 days) of which 80 children had severe or moderate dehydration (cases) and 160 children had 'no signs of dehydration' (controls). 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 of the following clinical factors with dehydration: duration of diarrhoea at hospital attendance (OR 1.9; 95%CI 1.05 to 3.4, p<0.05), stool frequency of more than five per day (OR 6.2; 95%CI 1.4 to 27.1, p<0.01), 'vomiting during episode' (OR 58.1, 95%CI 16.6 to 243.1) p<0.01), receiving oral rehydration therapy at home before admission (OR 10.7; 95%CI 3.0 to 44.6, p<0.01), receiving drugs at home before admission (OR 3.97, 95%CI 2.0 to 797, p<0.01) and 'wasted child' (OR 3.8; 95%CI 1.6 to 9.0, p<0.01). 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 due to ineffective preparation and administration of oral fluids. [EL = 2+]

Evidence summary

There were four relevant case-control studies all of good quality [EL = 2+] and despite the range and culture-specific risk factors investigated, these showed consistent results for widely applicable risk factors for the development of dehydration in children with gastroenteritis. In terms of demographic factors, younger children and those with malnutrition were at a greater risk of dehydration. The studies showed a consistent and strong association of severity of symptoms, that is, 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 oral rehydration 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 likely 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 birth weight 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 breast feeding was associated with a reduced risk was also potentially important.

Recommendation on clinical assessment

Recognise the following as being at increased risk of dehydration:

- children aged less than 2 years of age, with even greater risk for those aged less than 6 months
- infants who were of low birth weight
- children with more than 5 diarrhoeal stools in the previous 24 hours
- children with more than 2 vomits in the previous 24 hours
- children who have not been offered or have not been able to tolerate supplementary fluids prior to presentation
- infants in whom breastfeeding has stopped during the illness
- children with signs of malnutrition.

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 was a systematic review of diagnostic studies while the second cohort study compared digitally measured capillary refill time (CRT) with conventional CRT and overall clinical assessment.

The systematic review [74] 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 of age. After a systematic literature search of the MEDLINE database, additional searches were conducted on the individual symptoms and signs, Cochrane library, 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 effect model was conducted only if more than two studies evaluated a specific diagnostic test. [EL = 3]

Though the authors report 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 (kappa values between 0.46 and 0.57). Three studies reported on agreement among clinicians but wide variation was seen in the results for the various signs. Prolonged capillary refill had kappa values ranging from 0.01 to 0.65, while absent tears had values from 0.12 to 0.75. For rest of the signs, the level of agreement was either just better than the chance agreement (k value between 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 decreases the likelihood of detecting dehydration though 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 statistically insignificant LR's for a number of symptoms including history of vomiting and diarrhoea (severity), decreased oral intake, and a previous trial of clear liquids. 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

Results of the test characteristics of various signs are given in Table 4.1. Three signs had statistically significant pooled positive likelihood ratios in detecting 5% dehydration – capillary refill time (4 studies, +LR 4.1; 95%CI 1.7 to 9.8), abnormal skin turgor (4 studies, +LR 2.5; 95%CI 1.5 to 4.2) and abnormal respiratory pattern (4 studies, +LR 2.0; 95%CI 1.5 to 2.7). Sunken eyes and dry mucus 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 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 positive likelihood ratio (95%CI too wide to draw conclusions). The 95%CI for the positive and negative LR's for increased heart rate, sunken fontanelle in young infants, and an overall poor appearance included the null value.

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

Finding (number 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 mucus 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 1.04)	0.45 (-0.1 to 1.02)

[a] Point estimate from individual studies

A second prospective cohort study [75] aimed to determine whether capillary refill time (CRT) measured using a digital device (DCRT) could determine the presence of significant dehydration. The study population comprised of 83 children (aged one month to five 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 graphic 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 (≥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 area under the ROC for detecting presence of dehydration ≥ 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 positive LR of 11.4 (95% CI 5.4 to 22). Conventional CRT showed better results for specificity (88% versus 81%) and positive LR (4.5 versus 4.1) compared with clinical assessment, but its sensitivity was only 54% compared to 77% with clinical assessment scale. [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 a tabular manner as below:

Table 4.2 Classification by Armon K et al [17]

No dehydration	Mild-moderate dehydration	Severe dehydration

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: Dry mucous membranes (be wary in the mouth breather) Sunken eyes (and minimal or no tears) Diminished skin turgor (pinch test 1–2 sec) Altered neurological status (drowsiness, irritability) Deep (acidotic) breathing	Increasingly marked signs from the mild-moderate group plus: Decreased peripheral perfusion (cool/mottled/pale peripheries; capillary refill time >2 sec) Circulatory collapse

Table 4.3 Classification by WHO [76]

No dehydration	Some dehydration	Severe dehydration
Not enough signs to classify as some or severe dehydration	Two or more of the following signs: - restlessness, irritability - sunken eyes - drinks eagerly, thirsty - skin pinch goes back slowly	Two or more of the following signs: - lethargy/unconsciousness - sunken eyes - unable to drink or drinks poorly - skin pinch goes back very slowly (≥2 seconds)

Table 4.4 Classification by ESPGHAN [77]

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 & 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

Table 4.5 Classification by American Subcommittee on Acute Gastroenteritis [5]

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

Variable	Mild, 3% - 5%	Moderate, 6% - 9%	Severe, ≥10%
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/hour	<< 1 mL/kg/hour
Thirst	Slightly increased	Moderately increased	Very thirsty or too lethargic to indicate

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.

Though 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 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 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 (≥10%), with an implication that it was possible to make such distinctions based 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 ≥ 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 clinical 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 did recognise 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, was that the scheme was all that was required to guide fluid management (see Chapter X Fluid Management). 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 intravenous fluid boluses (Section 5.4, Chapter 5 on fluid management) 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 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 (e.g., 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 it 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 difficult 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, Chapter 5 on fluid management)

The GDG identified several 'red flag' signs in dehydration whose presence should alert the clinician to a risk of progression to shock. These were the presence of irritability or lethargy, sunken eyes, a sunken fontanelle in infants, tachycardia, tachypnoea, and reduced skin turgor. Children with such red flag signs required 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 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 (Chapter 5 on fluid management), 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 intravenous fluid therapy 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 (GP, community children's nurse, e.t.c.). Where there were concerns about a parent's ability 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.

Recommendations on detection and assessment of dehydration

During direct or remote assessment ask whether:

- the child has seemed to the carer to be unwell
- there has been excessive or unaccustomed irritability or lethargy
- the child has seemed unusually thirsty
- there has been a reduction in urine output
- the child's appearance has changed (e.g., sunken eyes)
- the skin colour is normal
- the hands and feet are warm.

Assess hydration with Table 4.6 in order to:

- classify children as non-dehydrated, clinically dehydrated or shocked
- use red flags as warning signs for increased risk of progression to shock.

Table 4.6 Candidate symptoms and signs available for the comprehensive assessment and classification of dehydration.

	No clinically detectable dehydration	Clinical dehydration This category represents a spectrum of increasing dehydration severity. With worsening dehydration clinical manifestations may be expected to become more numerous and severe	Clinical shock (a combination of features shown in this column must be present to determine a diagnosis of shock)
	Symptoms (remote and face-to-face assessments)		
Clinical feature of dehydration	Well child	Perceived to be unwell or deteriorating[a]	
	Normal conscious state	Excessive or unaccustomed irritability or lethargy	Depressed conscious state
	Normal level of thirst	Increased thirst	
	Normal urine output[b]	Decreased urine output[b]	
	Normal skin colour	Normal skin colour	Pale or mottled skin
	Warm hands and feet	Warm hands and feet	Cold hands and feet
	Signs (face-to-face assessments only)		
	Normal conscious state	Irritability or lethargy[a]	Depressed conscious state
	Normal skin colour and warm peripheries	Normal skin colour and warm peripheries	Pale or mottled skin and/or cold peripheries
	No sunken eyes	Sunken eyes	
	Moist mucous membranes[c]	Dry mucous membranes[d]	
	Normal fontanelle[c]	Depressed fontanelle[e]	
	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)

Red flags may help identify children at the more severe end of the dehydration spectrum in whom there is an increased risk of progression to shock, and for whom referral to hospital should be considered.

[a] Based on parent/clinician global assessment

[b] The presence of this symptom may help to rule out dehydration, but did not have sufficient diagnostic utility to do so in isolation

[c] Except after a drink

[d] Except mouth breather

[e] Relevant to younger infants, the fontanelle becoming progressively smaller and usually closing by 18 months

Notes on how to use this table:

- Symptoms and signs have been separated since only the former are available for remote (telephone) assessment.
- Symptoms and signs need to be interpreted in the context of the presence of risk factors for dehydration and the social and family circumstances.
- The distinction between 'clinical dehydration' and 'red flag dehydration' is not absolute and requires clinical judgement. If there is doubt, the child should be managed as for the more severe end of the spectrum.

Research recommendation

Studies should be undertaken to evaluate the diagnostic accuracy of symptoms and signs in children with varying degrees of dehydration using rehydrated weight as the gold standard.

Studies and audits should be undertaken to assess the effectiveness and acceptability of the novel clinical hydration assessment scheme and approach to ORT recommended in this guideline.

Why is this important?

Previous practice and guidelines have often implied that it is possible to determine the severity of dehydration with some accuracy based on the detection and evaluation of various clinical manifestations. Following a careful review of published research, the GDG concluded that there was little evidence to support this assumption. Many proposed strategies for evaluating the degree of dehydration were based on subjective and arbitrary criteria. The GDG concluded that a simpler approach to clinical evaluation was both practical and sufficient. It was merely necessary to classify children as being 'without clinical evidence of dehydration', 'clinically dehydrated' or 'shocked'. The only caveat was that a number of specific clinical manifestations ('red flags') might point to a risk of progression to shock. The GDG recommendations for fluids management were then directly linked to this assessment strategy. Those with clinical dehydration should be given ORT in a fixed volume (50 ml/kg over four hours). Regular re-evaluation during the process of ORT would determine whether the child required additional fluid to replace their deficit. Those with shock should receive IVT. The GDG believed that this approach to assessment and fluid management was both rational and safe. It would have the important merit of being simple to implement. However, the GDG recognised this was a novel approach and it would be important to evaluate its effectiveness and acceptability in everyday practice.

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

Hypernatraemic dehydration may be defined as dehydration associated with a serum 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, cool peripheries, 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 Africa [78] 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 one 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 less than 6 months old ($p<0.01$) compared to 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 dehydration 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 serum sodium concentration.

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 any of the following signs are present:

- jittery movements
- hypertonicity
- hyperreflexia
- convulsions
- drowsiness or coma.

4.2 Laboratory investigations in assessment of 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 1980–90s, used a non-comparative study design and did not give adequate data to calculate the incidences. Finally 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 have been 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 United Kingdom [57,58,54] one from Turkey [79], and one retrospective case series from the USA [80]. All the three studies from United Kingdom have already been included previously under Section 3.2.1.

The first United Kingdom study [54] included 1148 children less than 16 years of age admitted to a sub-regional infectious disease hospital with a diagnosis of gastroenteritis over a one year period. Of the admitted children 55% (635/1148) were aged less than one year while 5% were more than 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) children 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 to those who were not dehydrated (n = 1047): hypernatremia (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 study from UK [57], 447 children aged less than two years and admitted to a hospital with gastroenteritis were recruited over a one year period. 74% of the children were less than 1 year of age and two-thirds of under-1 year old were less than 6 months of age. The overall incidence of moderate to severe dehydration (assessed clinically) was 14%. Hypernatraemia (sodium levels ≥ 150 mmol/l) occurred in 0.8% cases, 8% had raised urea concentration (> 6 mmol/l), and 3% had bicarbonate concentration ≤ 15 mmol/l. However it was not specified if biochemical abnormalities were found only in children with moderate to severe dehydration. [EL = 3]

Another UK study [58] included 215 children admitted to four paediatric units in South Wales with gastroenteritis over a one year period. The age of the study population ranged from 2 weeks to 9 years and 61% children were less than one year of age. 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% children (76/215) on clinical grounds. 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% children had acidosis with bicarbonate levels < 15 mmol/l. [EL = 3]

The study from Turkey [79] aimed to investigate the relationship between blood glucose and serum electrolytes since it was hypothesised that changes in blood glucose levels during diarrhoea complicates 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 – less than 2 years of age 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. Hypernatremia (sodium levels > 150 mmol/l) was present in 7.6% of all cases and hyponatremia (sodium levels < 130 mmol/l) in 3.4%, while 48% children had bicarbonate levels < 15 mmol/l. 4.2% of children were noted to have potassium levels < 3 mmol/l. Hyperglycaemia (blood glucose levels > 140 mg/dL) was observed in 10.9% 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 to 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 aged less than 2 years with bicarbonate levels < 15 mmol/l compared to those with higher bicarbonate levels (> 15 mmol/l). A positive correlation was found between blood glucose and serum sodium levels in children less than 2 years of age 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. [EL = 3]

A retrospective case series from the USA [80] 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 intravenous fluid bolus. Hypoglycaemia was defined as serum glucose concentration less than 60 mg/dl (3.3 mmol/l). Medical records of 196 children (younger than 5 years) admitted over a one year period was reviewed and the mean age of the study sample was 23 months (SD 14 months). Overall 9.2% of children (18/192) were found to be hypoglycaemic but only one child had serum glucose levels less than 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 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 less than 18 mEq/l and 19% had BUN levels > 18 mg/dl, while in the group of children having normal glucose levels and dehydration, 92% had bicarbonate levels less than 18 mEq/l and 29% had BUN levels > 18 mg/dl. The difference between the two groups was statistically not significant for these two parameters. [EL = 3]

It is important to note that the investigators arbitrarily employed varying definitions for biochemical abnormality, and the clinical importance of these derangements should be taken into account while considering the results from these studies

The incidence of various biochemical disturbances as identified in the above 5 studies are tabulated below (Table 4.7). It is important to note that the investigators arbitrarily employed varying definitions for biochemical abnormality, and the clinical importance of these derangements should be taken into account while considering the results from these studies.

Table 4.7 Incidence of biochemical disturbances

Study reference	Number & age of children	Proportion of children (%) with dehydration	Proportion of children (%) with hypernatremia	Proportion of children (%) with hyponatremia	Proportion of children (%) with hypokalemia	Proportion of children (%) with urea concentration >normal	Proportion of children (%) with serum bicarbonate concentration <normal	Proportion of children (%) with elevated glucose
Conway et al [54]	*n* = 1148 Age range 0–10 years (37% were < 6 mths and 82% <2 year	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%) 11/101 (11%) dehydrated children and 6/1047 (0.57%) children without dehydration had plasma sodium concentration of >145 mmol/l) (hypernatraemia defined as plasma sodium concentration of ≥150 mmol/l)	NA	NA	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)	NA
Ellis et al [57]	*n* = 447 admissions made by 426 children under the age of 2 years (21 re-admissions) (75% <1 year old)	14% had moderate or severe dehydration	5 patients - no total number of patients stated 0.8% (hypernatraemia defined as serum sodium) (≥150 mmol/l)	NA	NA	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)	NA
Jenkins et al [58]	*n* = 215 Age range 2 wks to 9 years (61% <1 yr old)	15/215 (7%) with severe dehydration (>5%)	2/76 (2.6%) (hypernatraemia defined as plasma sodium concentration of >145 mmol/l)	17/76 (22%) (serum sodium concentration within the range 128–134 mmol/l)	NA	17/76 (22%) (serum urea concentration >6 mmol/l)	13/76 (17.1%) (serum bicarbonate concentration <15 mmol/l)	NA

Study reference	Number & age of children	Proportion of children (%) with dehydration	Proportion of children (%) with hypernatremia	Proportion of children (%) with hyponatremia	Proportion of children (%) with hypokalemia	Proportion of children (%) with urea concentration >normal	Proportion of children (%) with serum bicarbonate concentration <normal	Proportion of children (%) with elevated glucose
			(only 35% tested)	no definition of hyponatraemia given			(lowest value 9)	
Yurdakok et al [79]	*n* = 119 age range 2 mths to15 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)	NA	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 SR et al [80]	*n* = 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	No statement on the number of children with dehydration 207/528 (39%) received IV rehydration	NA	NA	NA	3/16 (19%) hypoglycaemic children had raised BUN (blood urea nitrogen) 44/150 (29%) non-hypo glycaemic 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-hypo glycaemic children had low serum bicarbonate (low bicarbonate level defined as <18 mEq/l)	NA

Accuracy of laboratory tests in detecting dehydration

Two studies were included to evaluate the diagnostic accuracy of laboratory investigations for evaluating dehydration – a systematic review and a prospective cohort study. The methodology of the systematic review [74] and results on 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 which 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 + LR's 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 quite wide. Acidosis was evaluated in four studies but these studies also used different cut-off points. Two studies defined acidosis as base deficit > 7 mEq/l and they reported +LR and –LR of 1.4, 1.8 and 0.4, 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). 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 USA [81] 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 to 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. 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-third of the children (50/75) had ≥ 3% dehydration while 21% had ≥ 5% dehydration confirmed by the weight-based criterion. No statistically significant correlation was found between urinary 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 (95% confidence limits containing 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]

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 to 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. Though 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. Another study 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 < 2 years with low bicarbonate levels. The last case series found 9.2% 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 to rest of the children admitted with gastroenteritis.

Evidence from the systematic review suggests that blood levels of bicarbonate more than 15 or 17 mEq/l (or absence of acidosis) are 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 urinary 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 incidence of clinically important biochemical disturbances in children with gastroenteritis. 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 United Kingdom the incidence of hypernatraemia was 1% or less, and those populations included children with severe dehydration. Increased serum 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 had also failed to provide evidence to support their use.

The GDG recognised that children with shock may develop a metabolic acidosis and in these children, monitoring of the blood gas has a clinically important role. The blood gas usually includes the pH, PCO2, bicarbonate, base deficit and lactate. Where acidosis is present it is important to consider the possible underlying mechanism. Hypovolaemia resulting in impaired tissue perfusion can lead to lactic acidosis. However, diarrhoea is often associated with significant bicarbonate loss and this is a common cause of acidosis. With hypovolaemia intravenous fluid boluses are required. With increased bicarbonate loss, spontaneous resolution usually occurs and fluid boluses are inappropriate and potentially harmful. To distinguish these types of acidosis, the GDG suggested that measurement of the anion gap could be helpful: $([Na^+] + [K^+]) - ([HCO_3^-] + [Cl^-])$ If the anion gap is increased in the context of dehydration this suggests an impaired tissue perfusion state. If the anion gap is normal, a bicarbonate losing state is likely to be responsible.

Recommendations on laboratory investigations in assessment of dehydration

Do not routinely perform blood biochemical testing.

Monitor serum sodium, potassium, glucose, venous blood gas, chloride, urea and creatinine concentrations if:

- IVT is required for shock
- there are clinical manifestations suggestive of hypernatraemia or acidosis.

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). Oral rehydration therapy (ORT) refers to the restitution of water and electrolyte deficits in dehydrated patients using an 'oral rehydration solution' (ORS). The term ORS is applied to special fluid formulations containing as essential ingredients an organic solute (e.g., 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 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 breast feeding and use of oral rehydration 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 six days or less at first presentation and had been breast feeding 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 '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 or home-made salt and sugar solution. Information on socioeconomic 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 analyzing 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 5 times higher in infants whose mothers stopped breast feeding compared to infants whose mothers continued to breast feed 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 to 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+] indicates that cessation of breast feeding in children with gastroenteritis is associated with an increased risk of dehydration. This study also suggests that oral fluid supplementation begun at home and given in good quantity is 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 a 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 the later in this chapter (Section 5.2), the GDG considered that it was reasonable to assume that liberal fluid supplementation is effective in the prevention of dehydration. Whilst it was recognised that some children may prefer other oral fluids, ORS has advantages (section X) and so should be used if possible for children at increased risk of dehydration (chapter 4, section X).

Recommendation on primary prevention of dehydration

In children with gastroenteritis but without clinical dehydration:

- continue usual fluids, including breast or other milk feeds
- encourage the drinking of plenty of fluids
- offer ORS as supplemental fluid for those at increased risk of dehydration:
  - children less than 2 years of age, especially those aged less than 6 months
  - infants who were of low birth weight
  - children with more than 5 diarrhoeal stools in the previous 24 hours
  - children with more than 2 vomits in the previous 24 hours
  - children with signs of malnutrition.

5.2 Treatment of 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 which 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 review [83] discussed below. Apart from the systematic review, another RCT conducted in children with severe dehydration [84] was included. The evidence was considered in three categories

1. ORT versus IVT for children with all degrees and types of dehydration
2. ORT versus IVT for children with severe dehydration
3. 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.

Evidence overview

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

A high quality Cochrane review [83] 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 (6 in the USA and 1 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 between 3 months and 5 years of age. One included children up to 17 years of age and three included newborn babies less than 14 days of age. 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 ORT group (n = 1015) than to IVT group (n = 796) because some trials included more than one ORT arm.

All the included trials used ORS solutions 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 4 of these nasogastric tube administration was employed if necessary. In two trials ORS was given exclusively by nasogastric tube, however 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 to IVT, and this difference was statistically significant (18 trials; RD 4%, 95%CI 1 to 7%) but with strong evidence of statistical heterogeneity ($p<0.001$). When sensitivity analysis was performed using a homogenous definition of 'failure' (limited to those with persistent vomiting, persistent dehydration and shock/seizures) the risk difference was reduced to 2% with the lower limit of the 95% CI including the null value (RD 2%, 95%CI 0 to 4%). Children treated with ORT had a significantly shorter stay in hospital compared to those treated with IVT (6 trials; WMD -1.2 days, 95%CI -2.38 to -0.02), but again there was evidence of significant heterogeneity. There was no statistically significant difference between the two groups for the other outcomes – weight gain at discharge, mean duration of diarrhoea, incidence of hyponatraemia or hypernatraemia, and 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% (5 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 was no difference between the two groups for the other complications and adverse effects - peri-orbital oedema, seizures and 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

(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 the hospital and those receiving IVT had a higher risk of phlebitis, but no significant differences were found between the ORT and IVT groups for the other complications (hypernatraemia, paralytic ileus, abdominal distension, peri-orbital oedema, seizures). Methodologically there was great variation between the trials with regard to the study population characteristics, composition of ORS and the modes of administration of ORS.

Cost-effectiveness evidence

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

The economic model in Appendix A assumes that as all children are ultimately re-hydrated, oral rehydration therapy (ORT) and intra-venous therapy (IVT) have equivalent clinical effectiveness. In this scenario, the cheapest option was generally also the most cost-effective. The base case analysis shows 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 mild to moderate dehydration.

5.2.2 ORT versus IVT for children with severe dehydration

Two randomised trials evaluated the effectiveness and safety of ORT versus IVT in severely dehydrated children. Both the trials were conducted in hospital settings – one in Iran and the other in Indonesia Due to the nature of the treatment and control protocols, blinding and allocation concealment was not done. One of these trials [84] was included in the Cochrane review described above.[83]

In the RCT from Iran [85], the study population included 470 children (1 - 18 months old) presenting with watery diarrhoea (> 10 ml/kg/hour), vomiting (> 6 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 intravenous 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, bicarb 35 mmol/l, chloride 65 mmol/l, glucose 70 mmol/l) was administered by nasogastric tube at a rate of 40 ml/kg/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, bicarb 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 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; WMD -0.70, 95%CI -1.16 to -0.24), 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 1 and 13 versus 7 respectively). Hyperkalemia occurred in 3 children in the IVT group and 5 in ORT group. However none of these observed differences in electrolyte abnormalities were statistically significant. Neither were any associated with clinical symptoms.

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 was no difference between the groups in the frequency of abdominal distension or peri-orbital oedema. There were seven deaths in all – two in the ORT group and 5 in 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 Indonesia [84] included 75 children (1 to 59 months old) 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 pre-determined random numbers. The ORT group received WHO recommended ORS by nasogastric infusion while the IVT group received Ringer's lactate solution. In both the groups fluids administration rates were in accordance with WHO recommendations (40 ml/kg in the first hour, 30 ml/kg in second, 20 ml/kg in 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 first 4 hours of treatment, while in the IVT group it was continuation of intravenous fluid longer than 4 hours due to excessive vomiting or seizures. [EL = 1−]

At baseline there were no 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 and 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 statistically not significant (p>0.05). No significant differences were seen for other outcomes studied – mean duration of diarrhoea, mean duration of vomiting and 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 was no difference 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 found no significant difference 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

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 if 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 6 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 lack of high quality evidence to compare the effectiveness and safety of ORT versus IVT in hypernatraemic dehydration. One poorly conducted RCT [EL1−] reported that a larger proportion of children treated with IVT experienced seizures compared with those given ORT. However the numbers of subjects was small and the difference was of borderline significance. Moreover this study did not report any other outcome.

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 statistically not 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 intravenous 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 to 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 the 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) 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, then 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 was a risk of adverse outcomes with ORT in these cases. For that reason, the GDG concluded that ORT was to be preferred.

Recommendation on treatment of dehydration

Rehydrate children, including those with hypernatraemia, using ORS unless they are in shock.

5.3 Oral fluids – optimal composition and administration

While the properties of ORS promote its effective absorption, other fluids might also have a role in the management of children with gastroenteritis. Fluids other than ORS are often given to children with diarrhoea and the GDG considered this practice. This section also examined the evidence regarding ORS composition. There has been much debate regarding the optimal constituents and their concentrations in ORS. 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, 3 studies were finally

included under this section. Two reviews had compared high osmolarity/sodium ORS with low osmolarity/sodium ORS, while the third review compared glucose-based ORS with the rice-based ORS. No study was identified to provide evidence on the effectiveness of different types of oral fluids (other than ORS), different regimes of ORS 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 paediatricians [86] 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 for children with diarrhoea. Anecdotally such practice is common in the UK. Although ORS 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 in the treatment of dehydration. However one study [87] 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 flavored drinks, carbonated drinks. Sodium concentrations ranged from 0.1 – 251 mmol/l, potassium concentration from 0.0 – 65 mmol/l, and osmolalities ranged from 246 to 2000 mOsm/l. Among the 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 shows great variation in the concentration of sodium and potassium, and in the osmolarity 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 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 fluids do not usually contain appropriate constituents. ORS was considered the appropriate fluid for oral rehydration.

Clinical question
What is the most effective composition of ORS?

ORS 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 and on the relative efficacies of glucose versus rice starch as the organic constituent in ORS.

The composition of the original WHO-ORS (glucose 111, sodium 90, potassium 20, chloride 80, and bicarbonate 30 in mmol/l) was selected to allow for use of a single solution that would effectively treat dehydration secondary to diarrhoea caused by different 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 might be excessive.[88] From the 1970s efforts focussed on improving the efficacy of ORS 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 adopted in 2002 (glucose 75, sodium 75, potassium 20, chloride 65, and citrate 10 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 which compared the effectiveness of high osmolarity/low sodium ORS with low osmolarity/low sodium ORS or the glucose-based ORS with the rice-based ORS. Evidence on other types of ORS 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 UK and are not currently recommended by the WHO.

Evidence overview

Three systematic reviews have been included – two [89] [90] provide evidence relating to effectiveness of low sodium/osmolarity ORS versus high sodium/osmolarity ORS, while the third review [91] compared rice-based ORS with the glucose-based ORS.

One systematic review [89] compared the effectiveness of the previously recommended WHO ORS (osmolarity 311 mmol/l with 90 mmol/l of sodium) with reduced osmolarity ORS (osmolarity 250 mmol/l or less with reduced sodium) in the treatment of children with acute diarrhoea. Only RCT's 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 less than 130 mmol/l) during follow-up. Results from the various studies were pooled using the fixed-effect model. [EL = 1++]

Fourteen RCT's were included in this review and they were conducted in Egypt (2), Bangladesh (3), Mexico (1), Columbia (1), India (3), Panama (1) and USA (1). All the studies recruited children under the age of 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 osmolarity less than 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. Since stool output was measured in various ways using different units in the RCT's, their results were pooled and expressed as standardised mean difference.

Out of 14 trials, 11 reported the need for unscheduled intravenous therapy. 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 8 trials (n = 1996) showed a significant reduction in the need of additional IVT for children receiving the low-osmolarity ORS compared to children treated with the WHO recommended high-osmolarity ORS (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 (SMD -0.23, 95%CI -0.33 to -0.14). Hyponatraemia and vomiting during rehydration were reported in 6 trials each. Children treated with the reduced osmolarity ORS showed a lower tendency for vomiting (OR 0.71, 95%CI 0.55 to 0.92) compared with the WHO ORS group, but no 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 to IVT among well nourished children with gastroenteritis in developed countries, and this was followed by a comparison between high sodium content ORS and low sodium content ORS. 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 10 patients. A total of 13 trials were included in this review and all were conducted in the USA or Canada – 6 RCTs of ORT with IVT arms and 7 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 hypernatremia (serum sodium level > 146) and hyponatraemia (serum sodium level < 132) induced by the treatment. [EL = 1+]

Altogether eight trials (1 RCT with an IVT arm and 7 trials without 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 of 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 of 5% (95% CI 1.9% to 8.1%). However there was no statistically significant difference in the failure rates of the three groups treated with high, medium and low sodium content ORS. Only one trial with an IVT arm gave information on the cases of hypo and hypernatraemia. It reported 3 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 6 cases each in the medium and low sodium groups. Estimates of effect could not be calculated for incidences of hyponatraemia and hypernatremia because the total numbers of individuals in each group were not available. Moreover there was no significant difference between the high and low sodium content ORS for other outcomes (weight gain, volume, frequency and duration of diarrhoea, length of hospital stay).

A Cochrane review [91] compared rice-based ORS (50 – 80 g/l of rice powder) to the glucose-based WHO ORS (20 gm/l of glucose) for the treatment of diarrhoea. Trials were included only if the rice-based ORS 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 due to difficulty in measuring the stool volumes.

Of 22 hospital-based RCT's included for this review, 12 trials included children – 5 with cholera and 7 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 less than 6 months of age 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 and outcome measurement started before or after initial IVT. In six trials 1–15% of randomised patients were excluded from the final analysis, however these patients should have continued to be monitored and their data included using intention-to-treat analysis. Outcomes were analyzed separately for children with cholera and non-cholera diarrhoea. [EL = 1++]

Twelve studies (n = 2854) reported the duration of diarrhoea for children aged less than 5 years suffering from non-cholera diarrhoea. Results from the meta-analysis suggest that children receiving rice-based ORS had shorter duration of diarrhoea compared with those receiving the glucose-based ORS, but the difference was statistically not significant (WMD -1.26 days, 95%CI -4.4 to 1.9). There was also no statistically significant difference between the two types of ORS for stool output in the first 24 hours of the intervention (15 trials; WMD -4.3 g/kg, 95%CI -9.4 to 0.8), and the total stool output (9 trials; WMD -28.2 g/kg, 95%CI -52.4 to 3.9). For children with cholera, a significant reduction in the 24 hour stool output was seen with rice-based ORS (4 trials; WMD -67.4 g/kg, 95%CI -94.3 to -40.5). Only 1 trial (n = 48) reporting 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.

Evidence summary

There is evidence from one high quality systematic review [EL = 1++] indicating significant reduction in the need for unscheduled IV fluids for the treatment of dehydration in children with diarrhoea when using low-osmolarity ORS compared to the previously recommended high-osmolarity WHO ORS. Moreover the results suggest that low-osmolarity ORS 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 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 favor of either high or low sodium ORS for rehydration.

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

GDG translation from evidence to recommendation

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

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

Table 5.1 Compositions of WHO ORS and of ORS 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 pre-2002	311	111	90	80	20	-	30
WHO-ORS post-2002	245	75	75	65	20	10	-
Dioralyte (Aventis Pharma)	240	90	60	60	20	10	-
Electrolade (Baxter)	251	111	50	40	20	-	30
Rapolyte (Provalis)		110	60	50	20	10	-

There are no studies that compare the new (2002) WHO-ORS to 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 there has been suggestion that low sodium ORS might be associated with hyponatraemia. Whilst 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 products currently available in the UK were appropriate for use in ORT.

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

Recommendation on optimal composition of oral rehydration solution

Use low osmolarity ORS (240–250 mOsm/l) for oral rehydration therapy.

Clinical question
What oral fluid regimen should be used?

No studies were identified that compared the clinical effectiveness of different oral fluid regimes 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, nasogastric); the frequency of administration; time interval over which rehydration should be attempted; or the indicators for reintroduction of oral fluids after IV therapy.

Evidence overview

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

In the first multi-center trial [92] the efficacy of reduced osmolarity ORS was compared with that of the pre-2002 WHO ORS. 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 trial [93] compared oral glucose electrolyte solution with oral sucrose solution in equimolar concentrations using the WHO recommended electrolyte formula. In severely dehydrated children (fluid deficit ≥ 10% body weight), 70% of their estimated fluid deficit was replaced within the first 2 hours by IVT and further rehydration accomplished by ORT. The third trial [94] evaluated the safety and efficacy of glycine-based ORS compared with ORS containing no glycine. Severely dehydrated children in both groups were initially given IVT until blood pressure and pulse returned to normal, and then rehydration completed within 4 hours by giving either of the two ORS.

Evidence summary

There were no studies that provided direct evidence on the effectiveness of different 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 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 working example in Table 5.2). Children with red flag symptoms or signs would require frequent reassessment during rehydration, with adjustment of the deficit replacement depending on that assessment.

Table 5.2 Working example of oral rehydration strategy; a 12 month old, of weight 10 kg

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

[a] Maintenance Fluids[95]

Weight (kg)	ml per day	ml per hour
0–10	100 ml/kg	4 ml/kg/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

The use of a nasogastric tube to deliver ORS is common but not universal practice. It may allow oral rehydration of children who will not drink ORS. If children vomit ORS persistently continuous infusion through a nasogastric tube may improve tolerance but there are no studies on this method of administrating 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 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:

- treat with low osmolarity ORS
- give 50 ml/kg of ORS over 4 hours in addition to maintenance fluids
- administer the fluid frequently and in small amounts
- consider supplementation with their usual fluids (including milk feeds or water, but not fruit juices) if they refuse to take adequate quantities of ORS and do not have red flag symptoms or signs of dehydration
- consider administration of ORS via nasogastric tube if they are unable to drink ORS or vomit persistently
- monitor the response to ORT by regular clinical reassessment.

Research recommendations

Studies should be undertaken to compare the effectiveness and acceptability of nasogastric tube administration of ORS with IVT in those children who do not tolerate ORT

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 IVT, the rate at which intravenous rehydration should be performed, the option of changing from IVT to ORT to complete the rehydration process, and the choice of intravenous fluid.

Systematic literature search identified 381 publications and 26 articles were retrieved for reviewing. Secondary screening of these studies led to 4 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.

Clinical questions
Who should receive IVT for rehydration? When should patients on IVT change to ORT?

No studies were identified which gave direct evidence on the indications for IVT in children with dehydration. Likewise, no studies specifically addressed the matter of changing from IVT to ORT during the rehydration process.

Evidence overview

In the absence of any direct evidence to answer these questions, information was collected from various studies which had described fluid regimens in which ORS was introduced after a period of initial IVT in children with severe dehydration. The different fluid regimens used to rehydrate children with severe dehydration and/or shock is summarised in Table 5.3. Initial intravenous fluid was given (e.g., 20–40 ml/kg) and then ORT was introduced usually after about 1–2 hours to complete the rehydration process.

Table 5.3 Fluid regimens used in different studies

Study	Initial IVT	Oral fluid administration
CHOICE study group [92]	40 ml/kg/hour for two hours	Began once child was able to take fluids
Alam et al [97]	Within one to two hours according to WHO guidelines	Began after initial IV rehydration
Bhargava et al [98]	Ringer's lactate 20- 30 ml/kg/hour until blood pressure and pulse returned to normal	Following initial IVT, rehydration completed with oral solutions
Patra et al [99]	Ringer's lactate for 1 to 2 hours for those presenting with signs of hypovolaemic shock	Began after approximately 2 hours
Sack et al [93]	70% of estimated fluid deficit replaced in the first 2 hours	Began after 2 hours
Santosham et al [94]	40 ml/kg of Ringer's lactate until blood pressure and pulse returned to normal [94]	Rehydration completed within 4 hours by ORT.
Maulen-Radovan et al [100]	40 ml/kg/hour of Ringer's lactate solution until blood pressure and pulse improved and patients able to tolerate fluids	Hydration continued using assigned ORS

Evidence summary

No study was identified which gave direct evidence on the indications for starting IVT or the appropriate time for switching IVT with ORT in children with severe dehydration and/or hypovolaemic shock. Processes followed in various trials suggest that these children were initially rehydrated with IVT (Ringer's lacate 20–40 ml/kg/hour) over a period of 1–2 hours or until there was improvement in blood pressure and pulse volume. ORT was usually introduced after 2 hours of starting IVT to complete the rehydration process.

GDG translation from evidence to recommendation

The GDG fully accepted established practice with regard to the initial management of patients with shock.[101] Consequently all children with hypovolaemic shock due to dehydration required IVT. Patients with severe dehydration may be at risk of becoming shocked. As discussed in the chapter on assessment of dehydration, 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 ORT the child's state of hydration did not improve or showed 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.

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 is monitored carefully and regularly.

In current practice the GDG believed that once IVT is begun, children often remain in hospital for lengthy periods, e.g., 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 about 1–2 hours, with subsequent rehydration gives as ORT. Given the proven effectiveness of ORT, the GDG concluded that children who received initial fluid resuscitation or rehydration with IVT should complete the rehydration process with ORT if tolerated.

Recommendation on when to use IVT for treating dehydration

Use IVT for dehydration:

- if clinical assessment confirms or raises suspicion of shock
- if, despite appropriate ORT, there are signs of deterioration with red flag symptoms or signs of dehydration.

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 intravenous therapy 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 to provide evidence for the first part of the question. For the second part a good quality RCT was found which compared 0.9% saline + 2.5% dextrose (NS) with 0.45% saline + 2.5% dextrose (N/2) for the treatment of dehydration.

A prospective randomised study [102] was 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 to 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 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 0.9% saline + 2.5% dextrose (NS) or 0.45% saline + 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/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 compared with those with normal plasma sodium, but apart from this there were no 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, there was no change in mean plasma sodium after 4 hours (p=0.32), but in those with an initially normal plasma sodium there was a significant decrease in the sodium concentration (p<0.001). Hyponatraemic children given 0.9% saline had a significant increase in mean sodium concentration (p<0.001), but in those with an initially normal plasma sodium there was no significant change. [EL = 1+]

Evidence summary

There was evidence from one RCT [EL1+] to suggest that rehydration with 0.9% saline IVT leads 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 intravenous rehydration should be performed. For the second part of the question three papers have been identified.

Evidence overview

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

The first was a prospective study with historical controls conducted in Australia [103] 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 capillary refill time 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 <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/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 <2 years) over an 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

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 ED and re-presentation requiring admission within 48 hours of discharge from the ED. The outcomes were measured for moderately dehydrated patients as well as for mildly dehydrated patients. Patients having rehydration via the intravenous 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 to 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 significant difference was seen for rates of re-presentation requiring admission within 48 hours of discharge from the Emergency Department. For mildly dehydrated patients of 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 USA [104] evaluating the efficacy of rapid IV rehydration in children with mild to moderate dehydration due to gastroenteritis in the hospital outpatient department. Criteria for inclusion were age > 6 months, clinical diagnosis of acute gastroenteritis with exclusion of other causes, vomiting for less than 48 hours in duration with at least 5 episodes in the 24 hours preceding presentation, presence of normal serum sodium levels (130 to 149 mEq/l) and metabolic acidosis (serum bicarbonate < 18 mEq/l) at the time of presentation. Each patient received an infusion of 20 to 30 ml/kg isotonic crystalloid solution over 1 to 2 hours, followed by a trial of oral rehydration. Children who subsequently vomited were admitted for continued intravenous 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, 15% (6/42) were re-admitted due 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 to 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 between 1 and 6 years of age 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 rate of 10 ml/kg/hour for three 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]

Altogether 17 children (mean age 2.6 + 1.7 years) met the study inclusion criteria. All had vomiting for an average 2.1 + 1.2 days prior to presentation at the emergency department and 59% of them had diarrhoea for the preceding 1.9 + 1.9 days. Seven patients had at least 6% dehydration and 7/12 patients 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 high quality evidence available for the clinical effectiveness of rapid IV rehydration in children with gastroenteritis and moderate/severe dehydration. The first study with a historical control group [EL = 2−] suggested that rapid rehydration by ORT or IVT in moderately dehydrated children leads to a significant reduction in the hospital admission rate and an increase in discharge from the Emergency Department within 8 hours of presentation. No 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 intravenous 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 intravenous fluid should be given. An initial bolus of 20 ml/kg is advised for those with hypovolaemic shock.[101],[106]

Currently the main focus of discussion regarding fluid administration in patients with shock is on the optimal choice of fluid. This includes crystalloid versus colloid fluids, especially in relation to the septicaemic or critically ill patient. The role of albumin solutions in particular is controversial.[107],[108],[109] The GDG considered that for children with shock due to dehydration from gastroenteritis, 0.9% saline was an appropriate and readily available fluid for bolus administration. In this form of hypovolaemic dehydration, with 20 ml/kg bolus fluid administration, rapid reversal of shock would usually occur. Where there was not an immediate response, a further 20 ml/kg bolus should be given. However in the event of an unsatisfactory response it was important to consider whether other factors such as septicaemia might be responsible for the patient's state of shock.

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 has recommended the use of Ringer's Lactate. There has been much discussion and debate on the choice of intravenous maintenance fluids for children, particularly since the 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]

Isotonic fluids such as 0.9% sodium chloride with 5% glucose are now recommended for a wide range of circumstance in which there is a risk of hyponatraemia, while 0.45% sodium chloride with 5% glucose is recommended for most of the other clinical scenarios. Children with dehydration due to gastroenteritis are included in the high risk group because they diarrhoea causes both water and salt losses.

There has been some controversy regarding the NPSA recommendations. There have been concerns about a possible increased risk of hypernatraemia and hyperchloraemic acidosis with 0.9% sodium chloride. That solution provides salt more than is present in the usual oral intake. It appears that most children have no adverse effects from this increased salt load, but there are some who do.[112] For that reason the many indications for isotonic solutions proposed by the NPSA have not been universally

accepted . However for gastroenteritis has not been challenged as an indication, given the associated salt losses. Further the NPSA recommendations emphasise the importance of monitoring plasma electrolytes during intravenous fluid therapy. The GDG therefore accepted the NPSA recommendations in this matter. The GDG also considered that it was important that clinicians should not misinterpret metabolic acidosis as a sign of persisting shock. This could lead to administration of excessive fluid.[113]

There was a lack of evidence to support recommendations on the management of hypernatraemic dehydration. A slow correction has traditionally been advocated to reduce the risk of hyponatraemic encephalopathy. There is no evidence from randomised controlled trials to support the recommendation of a particular intravenous solution, although for severe hypernatraemia (plasma sodium > 160 mmol/l) the NPSA has advised the use of an isotonic solution. The GDG considered that any child with hypernatraemic dehydration should be managed taking account of the individual case, but careful monitoring of changes in plasma electrolytes, urine output and the clinical status during IVT was essential.

As with ORT, there is no precise method for establishing the exact replacement deficit for IVT. If a child is considered to have entered a state of hypovolaemic shock, it is generally accepted that they are probably at least 10% dehydrated. This equates to a loss of 100 ml/kg of fluid in need of replacement. For those who are dehydrated but without shock, a volume of 50 ml/kg was considered by the GDG to be an appropriate initial volume for replacement (similar to the volume recommended for ORT). There was no evidence regarding the time period over which this intravenous deficit fluid deficit replacement should be given. Traditionally intravenous fluid rehydration has been carried out over a period of 24-hours, or 48 hours in those with hypernatraemic dehydration.

To reduce the length of hospital stay, there has been increasing interest in more rapid intravenous rehydration strategies - so called 'rapid rehydration therapy'. The limited evidence available suggested to the GDG that children given rapid rehydration therapy could be safely discharged from the emergency department. However the reported volumes of fluid given during rapid rehydration therapy (30–40 ml/kg, equating to deficit replacement of only 3–4%) suggested that in fact the children must have been at the milder end of the dehydration spectrum.

The GDG was aware that a study based in the Emergency Department at the Hospital for Sick Children, Toronto, was currently recruiting children to a trial comparing intravenous rehydration regimes in those who have failed ORT. One treatment group was receiving an initial 20 ml/kg of intravenous fluid and another group 60 ml/kg over a period of one hour [114].

Whilst the GDG considered that in principle this approach might be successful, there was still uncertainty about the effectiveness and safety of rapid infusion of very large volumes of fluids. Therefore the GDG concluded that there was currently insufficient evidence to support the use of rapid intravenous rehydration therapy.

The GDG concluded that until further clinical trials on rapid rehydration were carried out, in keeping with conventional practice the aim for children undergoing rehydration with IVT should be to complete the process over a 24 hour period. For those with hypernatraemic dehydration rehydration should be over 48 hours. However in order to minimise the period of dehydration the GDG strongly advocated attempting to switch over to ORT to complete dehydration as soon as the child tolerated it. It seemed likely that this policy could greatly reduce the time spent receiving IVT.

Recommendations on intravenous rehydration therapy

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

If the child remains shocked:

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

If IVT is required for rehydration of non-shocked children:

- use 0.9% sodium chloride with 5% glucose as the initial infusion fluid
- give 50 ml/kg of intravenous fluid over 24 hours (48 hours in hypernatraemic dehydration) in addition to maintenance fluids

- give an additional bolus of 5–10 ml/kg of 0.9% sodium chloride with 5% glucose for each large watery stool passed
- monitor serum electrolytes
- consider monitoring acid/base status
- change to 0.45% sodium chloride with 5% glucose if hypernatraemia or hyperchloraemic acidosis develop.

Research recommendation

Studies should be undertaken in those who require IVT for rehydration:

- to compare the effectiveness and safety of 0.9% NaCl with 0.45% NaCl solution
- to determine the optimal duration for rehydration – 'rapid rehydration therapy' (e.g., 1–4 hours) versus the traditional approach of slow intravenous rehydration (e.g., 24 hours).
- to evaluate the a strategy of changing to ORT to complete rehydration after an initial short period of IVT.

Why is this important?

Most children with clinical dehydration should be treated with ORT, but some require IVT, for example because they do not tolerate ORT or because they develop hypovolaemic shock. It is agreed that those with shock should be given intravenous bolus treatment with 0.9% NaCl solution. The optimal choice of intravenous fluid solution for *rehydration* is less certain. It has been suggested that the use of 0.9% NaCl might be associated with a risk of hyperchloraemic acidosis, while 0.45% might increase the risk of hyponatraemia. These fluids should be compared in a randomised controlled trial. Rehydration with ORT is usually carried out rapidly, for example over a period of 4 hours. When children undergo rehydration using IVT it is traditional to replace the fluid deficit more slowly – for example over 24 hours. The consequence is that children remain dehydrated and in hospital for a considerably longer time period. It is important that studies are carried out to compare the effectiveness and safety of 'rapid rehydration' with the slower approach. Finally, it is important to determine whether following an initial short period of IVT it is effective and safe to attempt to complete the rehydration process using ORT. If so this might have advantages such as a shorter period of hospitalisation.

Clinical questions

Should children be given additional fluid to replace continued losses during IVT? If so, which fluid should be used and in what volumes?

Evidence overview

No study was identified to answer these questions.

GDG translation from evidence to recommendation

The GDG considered that in calculating the total fluid requirement for a child on IVT it was important to consider not only the amount required for deficit replacement and for normal maintenance, but also significant ongoing fluid loss due to diarrhoea. If there was persistent severe diarrhoea the child might fail to rehydrate or might experience a recurrence of dehydration. Unless there was careful monitoring the severity of diarrhoea might not be recognised in a hospital setting, and children with severe diarrhoea receiving IVT might be at risk. From a practical perspective it is usually difficult if not impossible to measure stool losses accurately. This is particularly so in infants and young children because urine and stool measurement cannot be readily separated. These young patients are already at increased risk of dehydration. The GDG agreed that a pragmatic approach was to give an additional 5–10 ml/kg of ORS or intravenous 0.9% sodium chloride for each large watery stool passed.

It was also agreed that efforts should be made to give ORS to children receiving IVT. If a child is able to tolerate orally, IVT should be stopped as soon as possible and further rehydration completed with ORT only.

Recommendation

During IVT, attempt introduction of ORT and, if tolerated:

- stop IVT and complete rehydration with ORT
- give 5–10 ml/kg of ORS for each large watery stool passed.

5.5 Preventing recurrence of dehydration

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 was rehydrated whether by ORT of IVT, it would be important to ensure that they receive adequate fluids for normal maintenance and if necessary to compensate for significant on-going fluid loss from diarrhoea. This frequency of dehydration recurrence had not been clearly established, but clearly recurrence was a possibility. Intuitively, it seemed probable that some children were at increased risk of recurrence, for example very young infants, those with continuing severe diarrhoea or those with persistent vomiting who might not tolerate oral fluids.

There were therefore many variables to consider, and each individual child should be assessed for risk and managed appropriately. No proscriptive 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 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 after each diarrhoeal stool and more recently giving 50–100 ml if < 2 years and 100–200 ml if > 2 years of age.[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 supplementary regimes were not necessary for most children. However, they should be advised for increased risk patients with continued passage of large watery stools. It was important to bear in mind that children who for some reason remained on IVT following rehydration could be at risk of recurrence, and they too might need supplementation.

Recommendations on preventing recurrence of dehydration

Following rehydration children should be encouraged to drink plenty of their usual fluids or feed.

If dehydration recurs ORT should be recommenced.

Following rehydration, in those at increased risk of dehydration, give 5–10 ml/kg of ORS following the passage of each large watery stool. These children include:

- children less than 2 years of age, with even greater risk for those aged less than 6 months
- infants who were of low birth weight
- children with more than 5 diarrhoeal stools in the previous 24 hours
- children with more than 2 vomits in the previous 24 hours.

6 Nutritional management

Introduction

Prior to the onset of gastroenteritis children will be receiving nutrition from a range of sources. They may be breast feeding, 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. Breast fed 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] Also breast fed infants may 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 breast feeding should continue, but other food (e.g. formula feeds or solid foods) should be discontinued until the child is rehydrated.[116,19,17] 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) breast feeding
b) cow's milk formula feeding
c) mixed feeding (bottle/formula and breast feeding)
d) solid food/weaning food

Out of 30 retrieved papers 3 studies were found to be suitable for inclusion and all of them had looked at breast feeding 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 a RCT assessing the effects of breast feeding during acute diarrhoea on clinical outcomes, while the other two papers were case-control studies investigating the risk of dehydration associated with discontinuation of breast feeding.

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 to 24 months, had moderate or severe dehydration and had been normally breast fed. 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 oral rehydration solution alone (n = 26) or oral rehydration solution plus breast feeding (n = 26) during the first 24 hours in the hospital. In the second 24 hours all children received breast feeding and oral rehydration solution. Children requiring intravenous therapy were given intravenous rehydration fluids until they had no clinical signs of dehydration and were then randomly allocated to receive one of the two rehydration regimes. 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 intravenous fluids and the number of children having vibrio cholera detected in stool swabs. Children receiving breast feeding plus ORS had, on average, passed five fewer stools than those receiving ORS 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 (ml per patient) during the early phase of diarrhoea (1570.4 + 112.5 versus 2119.2 + 192.1, $p<0.05$). However there were no significant differences between the two groups regarding duration of diarrhoea in hospital, stool output (ml/kg) and vomitus output (ml per episode). [EL = 1+]

A case-control study conducted in India [69] recruited 379 infants with acute gastroenteritis of less than 24 hours duration. This study is described in details under 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 oral rehydration solution during diarrhoea (OR 2.1; 95% CI 1.2 to 3.6, $p=0.006$). [EL = 2+]

Another case-control study conducted in Bangladesh [82] considered withdrawal of breast feeding 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 six days or less at first presentation and if had been breast feeding up to the time of onset of diarrhoea. 285 moderately and severely dehydrated children were recruited as cases and 728 children with no clinical signs of dehydration were recruited as controls. Detailed information about the population characteristics and the study methodology is described under 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 5 times higher in infants whose mothers stopped breast feeding compared to infants whose mothers continued to breast feed 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 breast feeding along with ORS compared to children receiving only ORS. However no significant difference was found between the two groups for the duration of diarrhoea and the amount of stool and vomitus. Two case-control studies did not address the question directly but their results indicate that continuation of breast feeding during gastroenteritis is 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 which encourages continuation of breast feeds during rehydration, but cessation of other milk and solid feeds. The GDG recognised that there was some evidence suggesting that breast feeding actually conferred 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 breast feeding even for a few hours could pose significant

difficulties for mother and child (e.g., discomfort, possible risk to maintaining breast feeding). For these reasons breast feeding should continue if possible throughout the period of rehydration.

With regard to milk formula feeds and solid foods, different considerations applied. Such feeds could result in a reduced rate of gastric emptying. Delayed emptying might increase the risk of vomiting and consequently of failed oral rehydration. The GDG considered that the nutritional significance of any milk or solid food taken in the 3–4 hour rehydration phase of therapy was 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 could be made to this in children without red flag symptoms or signs of dehydration. If such children would not take an adequate amount of ORS they could be given supplementary feeds with their usual fluid – generally milk or water. They should not be given fruit juices as these can cause increased diarrhoea.

Recommendation on feeding during rehydration

During oral rehydration therapy – typically a 4-hour time period:

- continue breast feeding
- other milk feeds should normally be withheld
- consider supplementation with the child's usual fluids (including milk feeds or water, but not fruit juices) if they refuse to take adequate quantities of ORS and do not have red flag symptoms or signs of dehydration
- withhold solid foods.

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 for 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 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 papers 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 refeeding versus full strength refeeding regimes. 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 refeeding period. For the last subquestion, 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 refeeding 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 multi-center RCT involving 12 European hospitals [118] 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) under the age of 3 years who were hospitalised with acute diarrhoea (> 1 but < 5 days duration). 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 or on intravenous fluids. After appropriate rehydration with ORS 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 only for 20 hours followed by their usual diet (late feeding group; n = 96). In addition both groups were offered ORS (10 ml/kg) for each watery stool. Breast fed children received ORS and diet in addition to breast feeding. On comparing the baseline characteristics of the two groups, it was found that there was a statistically significant difference 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 if these factors had been adjusted during the final data analysis. Moreover limited data was 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 to 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 was also no statistically significant difference 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 breast feeding per day, those who received more than a single dose of antibiotics, who had an episode of diarrhoea within 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 according to WHO guidelines, children were assigned to four dietary groups by block randomisation procedure. These groups were a) Group 1 (n = 31): full strength formula based on casein, sucrose, dextrin, maltose, soybean oil and cotton oil with a vitamin-mineral mix added, b) Group 2 (n = 29): half strength formula with same composition as above for the first 48 hours followed by full strength formula, c) Group 3 (n = 34): ORS continued for the first 48 hours followed by half strength formula for next 48 hours and then full strength formula, and d) Group 4 (n = 34): intravenous fluids (no oral fluids) for first 48 hours followed by half strength formula for next 48 hours and then full strength formula. Thus by day five, 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 two week period. The baseline characteristics of the four groups were similar but limited data was available for the outcomes. It was seen that though 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. One week after admission, weight increments in Groups 1 and 2 were significantly higher compared to those in Groups 3 and 4 (ANOVA p<0.005). When the combined Groups 1 and 2 were compared with combined Groups 3 and 4 at two weeks after admission, the difference in weight increments was again statistically significant (ANOVA p<0.004). The children in the former two groups gained on average 140 g more than those in the latter groups. However there was no statistically significant difference 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 (< 3 days duration), moderate or severe dehydration, no previous antibiotic treatment, 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 degree Fahrenheit. After initial rehydration with ORS or IVF (duration not given), children were randomly allocated (using random number table) to the two groups: Group A (late feeding group, *n* = 33) where children received only ORS for 24 hours followed by khitchri (culturally acceptable food made from rice, legumes and cottonseed oil) and half strength cow's milk formula, and Group B (*n* = 36) where children received khitchri and half strength cow's milk formula along with ORS 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 and 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 Israel [42] in a primary care unit involved 90 infants aged 1–12 months with acute watery diarrhoea (≤ 7 days duration) and mild dehydration. Excluded were babies less than 30 days of age, 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. In the early feeding group children were given ORS for 6 hours (50 ml/kg) following which parents were advised to continue the same feeding which was being given prior to presentation and alternate it with ORS (75 ml/kg every 18 hours). In the late feeding group only ORS was given for the initial 24 hours (200 ml/kg/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 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 and 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 ≤ 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 breast feeding was continued or in non-breast fed infants a feeding regimen adapted to age was given after 3–6 hours of initial rehydration with ORS 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 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 to the late feeding group at 7 days (+1.2% + 1.1 versus -0.01% + 0.9, p=0.01). Moreover the proportion of infants with weight loss (compared to 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 to the late feeding group (76.6% versus 32.6%, p=0.01). However there were no significant differences between the two groups regarding the frequency of stools per day, stool output during hospitalisation and 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 to late feeding. Results from three studies (two RCT's and one quazi-randomised trial) suggest that weight gain is higher in children who receive early feeding (with breast or cow's milk or solid foods) along with ORS compared to children who are 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 difference 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 refeeding regimes, while one RCT looked at the effect of introducing juices in the feeds of children after appropriate rehydration.

A RCT conducted in two hospitals in Guatemala and Brazil [122] recruited 159 boys aged 15 days to 6 months with acute diarrhoea (duration < 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 breast fed, who had systemic infections or who had other infections requiring specific additional treatments. Children with dehydration were initially rehydrated orally with the WHO ORS 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 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 formulae were prepared by a dietician who was not involved in the clinical management or data collection, and both the formulae was given in opaque bottles (150 ml/kg/day divided in 8 feedings). Maintenance therapy in the form of ORS 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 assessed on day 5 at the time of discharge. There was no significant difference 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, and 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 to the other group (310 + 130 versus 172 + 67, $p<0.05$). [EL = 1+]

A RCT from UK [123] recruited 62 infants under 6 months of age 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 for 12 hours, the infants were randomly allocated to receive either full strength refeeding (full strength cow's milk formula or breast milk, n = 30) or graded refeeding (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% infants (26/62) had recurrence of diarrhoea within seven days of refeeding but there was no significant difference between the two groups for the incidence 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 [50], 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: refeeding with full strength cow's milk (n = 16), clear fluids until diarrhoea settled followed by introduction of full strength milk (n = 16), and clear fluids until diarrhoea settled, followed by graded refeeding in increasing concentrations by a quarter strength every eight hours till full strength achieved (n = 14). Exclusion criteria were not defined and no details were provided about the process of randomisation, concealment allocation and 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 a RCT conducted in a hospital in Australia [47], 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 refeeding group (n = 31; half strength milk for 24 hours and then normal feeds) or immediate resumption of full strength milk and normal food (n = 28). The authors did not specify about the randomisation process, concealment of allocation or blinding. At the time of admission, the two groups of children were comparable regarding the 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 to graded refeeding group but this difference was statistically not significant (-0.02 + 0.25 kg versus -0.14 + 0.21 kg; $p>0.05$). The full 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 and lactose intolerance at the time of admission. After rehydration with IVF, the children were randomised to receive either immediate full strength cow's milk formula refeeding (n = 29) or graded refeeding of half strength for 24 hours, two-thirds strength for the next 48 hours, followed by 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 17.5% children (13/74) dropped out of the trial due to lactose malabsorption. The main outcome measure was duration of diarrhoea in days and there was no significant difference between the two groups (2.62 versus 2.46 days, $p<0.05$). [EL = 1−]

Sixty-eight infants who were admitted in a UK hospital [125] with acute gastroenteritis (of less than seven days) and mild or moderate dehydration were randomised to one of three refeeding groups. Following appropriate assessment and rehydration, the infants were randomised to either immediate full strength refeeding with cow's milk formula or graded refeeding (in quarter measures per 24 hours) with cow's milk formula or immediate full strength hydrolysed whey protein formula. There was no difference in the mean duration of hospital stay or 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. A quarter of the infants randomised to the whey formula, refused to feed with it. [EL = 1−]

An RCT conducted in Brazil [126] evaluated the effect of juice intake during acute diarrhoea. The trial included 90 male infants aged 4 to 18 months with an episode of acute diarrhoea (duration < 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 breast fed were excluded from the study. After treating rehydration orally with ORS 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 colored and flavored to resemble juice and the investigators were unaware of the three groups, but the process of randomisation was not explained. Plain water was offered ad libitum between meals to all infants. Children in all the three groups were similar in age, duration and severity of diarrhoea, presence of vomiting, and there was no difference between the groups for serum electrolyte levels and hematocrit values. Though the total energy intake was higher in the juice fed groups compared to the WA group (ANOVA, $p<0.05$), the duration of diarrhoea (in hours) after randomisation was significantly lower in the water group compared to the juices group (49.4 ± 32.6 AJ group versus 47.5 ± 38.9 WGJ group versus 26.5 ± 27.4 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 refeeding but there were differences between the trials regarding the method of graded refeeding and outcomes measured. However the evidence was consistent in that there was no harm in giving immediate full

strength refeeding with cow's milk formula following rehydration and also no benefit of graded refeeding over immediate full strength refeeding. Two trials found evidence of increased weight gain with full strength formula but the difference was statistically not significant.

Result from one trial suggests that giving juices to children after rehydration prolongs the duration of diarrhoea compared to water. Though children receiving juices had a higher weight gain, the difference was statistically not significant.

6.2.3 Reintroduction of solid foods

Evidence overview

There were seven RCTs which describe mixed diets. All the studies involved 100 participants or less (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 to 36 months admitted to hospital after presenting to outpatients with a history of acute non-bloody diarrhoea of less than seven days duration. Children were excluded from the study of they were exclusively breast fed, had a temperature of over 102 degrees, had any systemic illness (including pneumonia, meningitis, 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 or IV Ringer's lactate and then randomly assigned (computer generated sequence and allocation of treatment by drawing lots) to either the dowdo diet (whole wheat 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 were later withdrawn from the study and there were three treatment failures (two from khitchri group and one from the dowdo group). The two groups had similar characteristics at the start of the study. Outcomes were assessed over 5 days. No significant differences were seen between the two diets in stool weight (males only), stool frequency, caloric consumption/kg, total weight change and duration of hospital stay. However, mothers reported 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 to 24 months if they had acute diarrhoea (>3 stools/24 hours) of less than 96 hours duration prior to hospital admission. Children were excluded if they were breast fed more than once a day, had significant wasting, oedema, systemic illness affecting enteral feeding or if they 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 (2 in the rice bean group and 3 in the rice soy group). Energy consumption was similar up to day four, but days four-six, consumption was greater in the rice bean diet compared with the rice soy diet (p<0.02). There were no differences in the overall difference in weight gain between the two diet groups, or in 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 versus121 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 and three or more liquid stools in 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 intravenous 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 aged under1 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) however there were no statistically significant differences in weight changes 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 (p<0.01) or dilute (p=0.05) porridge groups, but there were no further differences amongst groups up to day 5. [EL = 1+]

The second study [130] 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 for <14 days - parental observation- 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 one day and children requiring nasogastric feeding tubes. Rehydration therapy (according to WHO guidelines) and 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) or 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 was no statistically significant difference 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 was greater in amylase digested group compared to the normal porridge group (42% more, p=0.003). There were no other differences in energy intakes between the groups and no mother/child preference was stated. [EL = 1+]

Three of the RCTs compared solid food with soy formula.

Infants aged 5–24 months with diarrhoea (>3 stools/day) for less than 96 hours were recruited in a trial conducted in Peru.[131] Exclusion criteria were the use of antibiotics (>1 dose), breastfeeding (1 feed/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 four, pea flour, carrot flour, soybean oil, cotton seed oil and sugar) (*n* = 28) or potato milk diet (potato flour, dry whole milk, carrot flour, soybean oil, cotton seed oil and 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 (p=0.01) 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 was no statistically significant difference in energy intake or weight gain between the three groups at any point. However there was a significant decrease in the duration of diarrhoea with the wheat peas diet and potato milk diet groups compared with the soy formula (57 hours versus 55 hours vs 154 hours respectively p=0.005). [EL = 1−]

The second study [132] was conducted in Nigeria and recruited boys aged 6–24 months who had been hospitalised for acute watery diarrhoea (defined as >3 liquid stools/day for less than 72 hours). Those with gross faecal blood, who had received > 1 dose of antibiotics, who were breast feeding more than once a day or who were under 2 SD of the weight for length reference data from the US National Centre for Health Statistics, were excluded.). Oral rehydration therapy (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 and 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 to 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 to 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 to the soy formula diet (42 hours versus 104 hours, p<0.001). Mean weight change data was poorly described data was 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 >3 liquid stools/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 (eg pneumonia, 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 Centre for Health Statistics). Oral rehydration therapy (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 to the soy group (25 hours versus 67 hours, $p<0.001$). Although at day 1, infants were heavier in the mixed diet versus the soy group, by day two, and up to day six there was no significant difference in weights between the two groups. [EL = 1−]

Evidence summary

Seven RCT's were examined which compared a wide range of mixed diets. These studies were based on rice, lentils, porridge, soy, and maize. No single solid diet or composition of solid diet in terms of carbohydrate, protein or fat was shown to be more effective that another for the post rehydration, maintenance phase for children with acute diarrhoea. The diets examined were specific to different regions in the world. Although these diets confer no advantage, they did not have any harmful effect. However, the porridge diets suggest that a thinner food consistency aids consumption and acceptability. In the studies with soy formula, the data suggest that the soy formula may prolong the duration of diarrhoea compared to solid foods.

6.2.4 The role of special milk formulas

Evidence overview

There were three RCTs which 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 refeeding 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 sixty five infants aged between 6 to 34 months (mean 14.7 months) admitted to a hospital in Finland with acute gastroenteritis and mild or moderate dehydration [49]. Exclusion criteria were not presented. Following assessment and 6–10 hours oral rehydration therapy, children were randomised to either a milk containing diet (n = 38) or a milk-free diet (n = 27) and followed up for three days and then at a outpatient appointment one 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 report significantly more vomiting amongst the children receiving milk compared to those with a milk-free diet ($p<0.01$). Twelve children in the milk-free diet vomited a total of 24 times compared to 4 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 (>4 watery stools /day with a total duration of one week or less) and mild or moderate dehydration[43]. Exclusion criteria were >50% milk intake from breast feeding, no use of lactose milk/formula prior to illness, diarrhoea caused by E histolytica, antibiotic therapy in the 48 hours prior to admission chronic malabsorption syndrome or refusal of consent from parents. Children received IV and oral rehydration therapy 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) 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) compared to the lactose formula group (mean 2.3 SD 1.0). There were three treatment failures – one in the lactose free formula group and two in the lactose formula group. The main outcome outcomes were mean duration of diarrhoea and body weight increment. No differences were seen in either outcome measure between the groups. [EL = 1−]

Eighty male infants (age range 3 -24 months) admitted to hospital with acute diarrhoea (< 7 days duration) 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 oral rehydration therapy over four hours and then were randomly assigned (block randomisation, coded identically packaged formula tins) to either lactose free (n = 40) or lactose formula (n = 40) following appropriate rehydration and followed up for 7 days. These formulas were given in addition to ORS (post 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 to the lactose formula group (77 hours versus 97.5 hours p=0.002) and a greater weight increase in the lactose free group at day one (p=0.005), but there were no statistically significant differences in weight prior or subsequently to this. [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 one, there were no cases of recurrence in either group. On day six, there was significantly greater number of recurrence cases in the lactose compared to the non-lactose group (15(21%) versus 4(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 Africa [44] with acute gastroenteritis (>3 liquid or watery stools/day of less than 7 days duration) and dehydration. Exclusion criteria were diarrhoea > 7 days duration, ORS administration for 5 days prior to admission, modifications to lactose consumed in the diet or withholding of food, inability to tolerate feeds, 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 measure was 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 (of 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 breast fed, 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 was no significant differences in weight gain between the two groups at 14 days nor any difference in the median duration of hospital stay (not all infants were hospitalised). However the duration of diarrhoea was significantly less in the soy compared to 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 refeeding

Early versus late feeding with a soy formula was investigated in a trial involving 56 infants between 2 – 12 months (mean 6 months) with acute diarrhoea (>5 watery stools in previous 24 hours of less than 7 days duration) and mild dehydration (>7% dehydration) seen in a USA hospital outpatient

department or a private health clinic.[137] Exclusion criteria were not presented. Following assessment, infants were randomised (using random number tables, no allocation or masking details provided) to either ORS plus soy formula for 24 hours (n = 29) or ORS 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 three groups had similar characteristics at the start of the study. There was a significantly greater percentage resolved illness in the early group versus the late group at 48 and post 48 hours time point (21% versus 12%, p=0.02 and 6% versus 15%, p<0.01). Duration of diarrhoea was also significantly shorter in the early group compared to the late group (2.0±0.2 versus 2.7±1.3, p=0.02). However, there were no significant differences in weight gain between the groups at 24 hours, resolution of illness or two weeks post therapy. [EL = 1−]

Cow's milk formula versus a special formula

Sixty infants less than 2 years of age (mean 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 nongastrointestinal 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 on in the cows' milk group. There was no difference in the duration of diarrhoea between the two groups. There was a significant difference in 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 (>4 watery stools in previous 24 hours of less than 96 hours duration) and mild or moderate dehydration were recruited in a trial[139]. Criteria for exclusion were shock, malnutrition, >2 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 and then randomised (using block randomisation and sealed envelopes) to either cow's milk (n = 37) or an experimental soup (n = 36) (59% hydrolysed plantain, 27% chicken meat with skin and 14% coconut oil). The two groups had similar characteristics at the start of the study except that children in the cows' 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 one 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 was no difference in these outcomes between the two groups. [EL = 1−]

Evidence summary

From the data available, there is no significant evidence to suggest a benefit of using a non-lactose formula (whether treated cow's milk or soy formula) over a lactose containing formula in the refeeding period following rehydration. There is insufficient evidence for any other special formula to make a definitive statement. Two comparative RCTs of soy formula suggest that early compared to late refeeding with soy formula reduces the duration of diarrhoea but has 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 believe 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 was 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. Available evidence shows no benefit from such formulas in studies continued for up to 7 days.

There has also been a belief that cows 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 that, provided weight gain is adequate, this is recognised as a normal phenomenon. To use specialised formula feeds is unnecessary, expensive and might cause parental concern.

Recommendation on feeding following rehydration

Following rehydration:

- give full-strength milk from the outset
- reintroduce the child's usual solid food
- avoid giving fruit juice until diarrhoea has stopped.

7 Antibiotic therapy

7.1 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 to 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 to placebo and were included in this review.

7.2 Salmonella

Evidence overview

Four RCTs were identified.[141],[142],[143],[144]

The trials were conducted in USA [141], Taiwan.[142], Canada [143] and Colombia [144] Three trials had three treatment arms [141],[142],[143] and one trial [144] had two treatment arms, but as per protocol changed the route of antibiotic administration from IM to oral in the second year of the study. This allowed comparison of ampicillin (IM and oral) and amoxicillin to placebo and of azithromycin, cefixime, trimethoprim/sulphamethoxazole and ampicillin to no treatment.

In one study the treatment groups were comparable at baseline.[143] The children receiving antibiotics were significantly younger than those in other treatment groups in two trials.[141],[142] In one trial [144] children with *E. coli* were younger than other groups and more children with shigella had abnormal stool and clinical signs. Allocation concealment, sequence generation and blinding of outcome assessors was adequate in three trial [141],[142],[144], and not stated in one trial. None of the trials presented a power calculation.

One RCT [141] with three arms compared treatment with ampicillin (100 mg/kg/day) (n = 15), amoxicillin (100/mg/kg/day) (n = 15) or placebo (n = 14) given in 4 equal doses daily for 5 days for the treatment salmonella gastroenteritis (n = 45). [EL = 1+] The trial included children up to 8 years seen in hospital with acute diarrhoea and salmonella species isolated in rectal swab cultures. Parents reported clinical symptoms and took rectal swabs daily. Participants were followed up in clinic at day 2–3 and day 5–6, then every fortnight for 2 months.

A second three armed study [142] [EL 1+] 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. Participants were assigned to treatment with oral azithromycin 10 mg/kg/day, in one dose daily for 5 days (n = 14), cefixime 10 mg/kg/day, in 2 doses daily for 5 days (n = 14) or to no treatment (n = 14) and were followed up with weekly visits to clinic after completion of therapy until two consecutive normal stools were noted.

A third three-armed treatment trial [143] [EL = 1+] compared the effectiveness of trimethoprim/sulphamethoxazole, ampicillin and no treatment for the management of salmonella enteritis (*n* = 36).

Children were randomised to treatment groups if they were aged between 10 months to 15 years and 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

Antibiotic regimes used were 20 mg/kg/day trimethoprim + 100/mg/kg/day sulphamethoxazole oral suspension 4 times per day for 7 days (*n* = 14) or ampicillin 100/mg/kg/day oral suspension or capsules 4 times per day for 7 days (*n* = 10) compared to no antibiotic treatment (*n* = 12)

During treatment, follow up was by daily physical examination and culture of stool specimens. After treatment had finished, 2 or 3 consecutive daily stool samples were taken for culture at 1 wk, 8 wks and 6 months. Family contacts also had stool cultures performed at admission and as for participants post therapy

One trial [144] examined the effect of ampicillin versus placebo on salmonella infection. [EL = 1+] 110 of 282 infants and children under 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 ampicillin or placebo suspension every six hours for 5 days).57 participants received either IM or oral ampicillin and 53 received either IM fructose or oral placebo.

7.2.1 Oral ampicillin versus placebo or no antibiotic treatment

Two trials made this comparison[141],[143].

One trial [141] reported no significant differences between the ampicillin group and placebo group for the mean number of days until diarrhoea stopped. However, compared to placebo, participants receiving ampicillin did have a significantly reduced mean number of days until the first negative culture and mean number of days until diarrhoea improved (WMD = -10.00 [95% CI -16.88 to -3.12] and WMD = -1.20 [95% CI -1.65 to -0.75] respectively). The day of the first negative culture was defined as the first of at least two consecutive negative cultures. Excretion of salmonella continued for significantly longer in the ampicillin group compared to placebo (Days until last positive culture WMD = 20.40 [95% CI 13.49 to 27.31]

Results suggest that antibiotics did not curtail duration of diarrhoea compared to placebo, although they did reduce the time taken for symptoms to improve (no definition given). Salmonella continued to be excreted for significantly longer in the oral ampicillin group. Oral ampicillin significantly reduced the mean number of days until the first negative culture compared to those receiving placebo. [EL = 1+]

One trial [143] reported no significant differences between either antibiotic treatment group and the no antibiotic treatment group were noted for mean duration of diarrhoea after start of therapy (2.8, 3.1 and 3 days respectively), mean duration of hospitalisation after start of therapy (5.3, 5 and 6 days respectively) or mean duration of fever after start of therapy (3.2, 1.6 and 2.6 respectively). [EL = 1+]

Evidence summary

The results of one RCT suggested that antibiotic treatment with ampicillin did not shorten the duration of diarrhoea when compared to placebo. It did reduce the time taken for symptoms to improve, although no definition of improvement was given. Ampicillin significantly reduced the mean number of days until two consecutive negative cultures were obtained compared to those receiving placebo. However, salmonella excretion continued for a significantly longer time in the ampicillin group and [EL = 1+]

One RCT reported that oral ampicillin did not affect the duration of diarrhoea, fever or hospitalisation. [EL = 1+]

7.2.2 IM or oral ampicillin versus IM fructose or oral placebo

One trial [144] reported no significant difference between 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 five-day course of therapy. Although details of relapse in the placebo group are not presented, the authors assert that this finding was statistically significant (p=0.0253) and that fewer patients receiving IM antibiotics than those receiving either placebo (p=0.113) or oral ampicillin (p=0.0405) became short-term salmonella carriers (culture positive anytime after completion of therapy)

Evidence summary

One RCT comparing antibiotic therapy (oral or intramuscular ampicillin) with oral or IM placebo found that IM ampicillin protected children against relapse and carriage of salmonella infection significantly better than placebo or oral ampicillin [EL = 1+]

7.2.3 Amoxicillin versus placebo

One trial [141] reported no significant differences were found between amoxicillin and placebo for the mean number of days until the first negative culture, or for the mean number of days until diarrhoea stopped. However, compared to placebo, participants receiving amoxicillin did have a significantly reduced mean number of days until diarrhoea improved (WMD = -1.00 [95% CI -1.45 to -0.55]. Excretion of salmonella continued for significantly longer in the amoxicillin group compared to placebo (days until last positive culture WMD = 16.10 [95% CI 8.75 to 23.45])

Results suggest that antibiotics did not curtail duration of diarrhoea compared to placebo, although they did reduce the time taken for symptoms to improve (no definition given). However, salmonella continued to be excreted for significantly longer in the group receiving amoxicillin compared to those receiving placebo. [EL = 1+]

Evidence summary

Results from one trial suggested that amoxicillin did not affect the duration of diarrhoea. Although diarrhoeal symptoms improved more rapidly compared to placebo, children receiving amoxicillin continued to excrete salmonella for longer. [EL = 1+]

7.2.4 Azithromycin versus cefixime versus no treatment

One three armed trial [142] found no significant differences between azithromydin or cefixime compared to each other or no treatment for the mean duration of diarrhoea post-treatment, mean duration of fever post-treatment (days) and the proportion of patients with positive cultures at week 3 post treatment. [EL = 1+]

Evidence summary

One trial found that giving oral azithromycin or cefixime did not affect the duration of diarrhoea or fever or the salmonella carriage rate.

7.2.5 Trimethoprim/sulphamethoxazole versus no antibiotic treatment

One trial [143] reported no significant differences between either antibiotic treatment group and the no antibiotic treatment group were noted for mean duration of diarrhoea after start of therapy (2.8, 3.1 and 3 days respectively), mean duration of hospitalisation after start of therapy (5.3, 5 and 6 days respectively) or mean duration of fever after start of therapy (3.2, 1.6 and 2.6 respectively) [EL = 1+]

Evidence summary

One RCT found no differences the duration of diarrhoea, fever or hospitalisation in children given trimethoprim/sulphamethoxazole compared to those given no antibiotic[EL = 1+]

7.3 Campylobacter

Evidence overview

Three RCTs were identified.

All three trials were conducted in the 1980s and compared erythromycin treatment to placebo or no treatment for campylobacter enteritis in a total of 59 children. All trials reported adequate comparability of treatment groups at baseline. Two studies [145],[146] had adequate allocation concealment, sequence generation and blinding of outcome assessors. One study [147] did not present details of allocation concealment or sequence generation, and assessors were not blinded to treatment. Power calculations were not presented in any trial.

One RCT [145] conducted in South Africa examined the effect of erythromycin treatment for campylobacter-associated enteritis compared to placebo in infants aged 1–24 months. [EL = 1−] Results for all participants (*n* = 25) are discussed later, but those for children who were infected only with *Campylobacter jejuni* (*n* = 8) are presented here.

Children admitted to hospital with diarrhoea of <96 hours duration and who had not received any antimicrobial therapy for this illness were included in this study. Confirmation of C jejuni and any other infection was from microscopic and culture examination of stool samples. Participants were randomised to receive an oral suspension of either 40 mg/kg/day erythromycin (*n* = 4) or placebo (*n* = 4) in divided doses for 5 days. Follow up was by daily examination for one week.

Although the study was well conducted, causative organisms were identified retrospectively and only eight children with campylobacter infection alone were included, reducing the power of the study for these results. No 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 RCT [147] conducted in Canada recruited children of up to 12 years (and their household contacts) on the prospective identification of a positive, erythromycin sensitive stool culture of campylobacter. [EL = 1+] Children with symptoms of enteritis were randomised to no treatment (*n* = 12) or to treatment with 40 mg/kg/day erythromycin every 6 hours for 7 days (*n* = 15) and were followed up until the entire household had three consecutive negative (weekly) stool samples.

One RCT [146] conducted in Peru examined the effects of early erythromycin treatment for campylobacter-associated enteritis compared to placebo in children aged 3–60 months brought as outpatient for treatment of acute diarrhoea (*n* = 24). [EL = 1+]

Participants were randomised to receive 50 mg/kg/day erythromycin oral suspension (*n* = 14) or placebo oral suspension (*n* = 10) in 4 doses for 5 days. 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.

Outcome - Mean duration of diarrhoea
Two trials reported results for this outcome.

One trial [147] reported no significant difference in the mean duration of diarrhoea experienced by participants receiving erythromycin (3.2 +/- 1.7 days) or no treatment (3.8 +/- 4.0 days) (WMD -0.60 [95% CI -3.02 to 1.82] p=0.63). 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.

The second trial [146] found that the mean duration of diarrhoea was significantly lower in the patients receiving erythromycin (2.4+-0.4 days) compared to placebo (4.2+-0.3 days) (WMD = -1.80[95% CI -2.08 to -1.52]). However, the number 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]).

Outcome - Mean number of days until last positive /first negative stool culture

One trial reported findings for the last positive stool culture, and one for the first negative stool culture.

One trial [147] reported a significant difference 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).

The second trial [146] found that the mean number of days until last positive stool culture was significantly lower for those receiving antibiotics (0.5+-0.3 days) compared to the placebo group (2.2+-0.6 days) (WMD -1.70 [95% CI -2.10 to -1.30]). No significant difference was found in the proportion of patients in each group with a positive stool culture at 5 days (erythromycin 1/11 versus placebo 3/5, RR = 0.15 [95% CI 0.02 to 1.12])

Evidence summary

Of three available RCTs, one was too underpowered to detect any statistically significant differences in treatment with erythromycin or placebo. [EL = 1−] There were conflicting results from the two remaining studies. One (EL1+) found no difference between the groups in mean duration of diarrhoea. The second (EL1+) 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 reducing the mean number of days until last positive /first negative stool culture. [EL = 1+] However, it could not be established that erythromycin treatment caused fewer patients to excrete campylobacter at day 5 compared to placebo. [EL = 1+]

7.4 Yersinia

Evidence overview

One RCT was identified. This study [148]was conducted in Canada and examined the treatment of yersinia enteritis with trimethoprim/sulphamethoxazole compared with placebo (n = 45) (EL=1-). Participants were children under 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 first 7 days, then weekly thereafter. There was about 25% loss to follow up and results for only 34 children were presented. There were no significant differences between antibiotic (n = 18) and placebo (n = 16) groups for clinical outcomes (median duration of diarrhoea, the number of patients experiencing diarrhoea for <7 days and recurrence of diarrhoea). However, 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, P < 0.005) and the number of patients with positive stool cultures at end of treatment (erythromycin 2/18 versus placebo 13/16, P<0.001), both favoured antibiotic use. Yet, more participants taking antibiotics (7/18) had a bacteriologic relapse compared with placebo (0/16) (P<0.05)

Evidence summary

Evidence from one RCT suggested that erythromycin treatment compared to 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 bacteriologic relapses compared to placebo. [EL = 1−]

7.5 Shigella

Evidence overview

One RCT was identified. This study[144] compared the effects of ampicillin with placebo in infants and children under 2 years of age admitted to hospital in Colombia with diarrhoea as a major symptom.(*n* = 282). (EL1+). 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 ampicillin or placebo suspension every six hours for 5 days). Overall, 37 participants had shigella infection – 16 received ampicillin and 21 placebo. No significant differences were found between the treatment groups for 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 respectively). 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 placebo (<0.5 versus 2.6 days, P<0.05 ; <0.5 versus 1.6 days, P<0.05 respectively). 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 ; 0.9 versus 2 days, P<0.05). IM ampicillin was more effective in this respect than oral administration (0.4 versus 1.5 days, p <0.05).

Evidence summary

Patients treated with ampicillin for shigella took fewer days to become afebrile and to stop excreting the organism than those treated with placebo. IM was more effective than oral ampicillin in reducing the time to becoming stool culture negative. Ampicillin did not significant effect the time to improvement or cessation of diarrhoea [EL = 1+]

7.6 *Escherichia coli*

Evidence overview

The Colombian trial described above[144]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). [EL = 1+] In total 35 of 282 infants and children under 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 in 6 hourly doses for 5 days or 100/mg/kg in 12 hourly doses for 5 days) and 17 received either IM fructose or oral placebo in 6 hourly doses for 5 days. There were no 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

There were no significant differences between either ampicillin groups or between the ampicillin and placebo groups in the mean number of days until diarrhoea improved or ceased nor in the mean number of days until the patient became afebrile or culture negative. [EL = 1+]

7.7 Cryptosporidium

Evidence overview

A comparative trial [149] conducted in Egypt was identified that examined the effect of nitrazoxanide and co-trimoxazole compared with placebo for clinical and microbiological 'cure' of cryptosporidium infection. [EL = 1−] 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.

Of 1087 patients with diarrhoea examined in the out-patient clinic, 150 were found to have cryptosporidosis. 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 (nitrazoxanide, 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 significant difference in the number of children cured (21/24) following administration of nitrazoxanide compared to placebo (9/25) (RR 2.43 [95% CI 1.41 to 4.19] p= 0.001). A 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

There was evidence from one potentially biased controlled trial that nitrazoxanide but not co-trimoxazole was effective in achieving a microbiological cure in children under 12 years of age with diarrhoea of cryptosporidium infection. [EL = 1−]

7.8 Treatment without prior identification of a pathogen

Evidence overview

4 RCTs were identified as relevant

2 studies were conducted in South Africa [150],[151] and two in Mexico [152],[153]

Three trials had two treatment arms [150],[151],[152] and one trial had three treatment arms [153]. The method of randomisation was adequate in two trials [150],[151] and not reported in two.[153],[152] The outcome assessor was blinded in three studies[150],[151],[152] , but not in one trial[153] The proportion of patients randomised but lost to follow-up was reported in all the studies (<20%). None of the trials included a sample size power calculation Comparability of the groups at study entry was adequate in three studies [150],[151],[152] although in one study [152] 50/141 participants had body weight under the 3rd percentile for age according to Mexican standard criteria. In one trial [153] patients receiving furzolidone had fewer days with diarrhoea prior to recruitment compared to patients receiving either trimethoprim/sulphamethoxazole or no antibiotic treatment (p<0.02) and

Across the four studies, data from 378 children (aged 2 months to 7 years) suffering from gastroenteritis was collected.The following comparisons were investigated : trimethoprim/sulphonamide versus placebo, trimethoprim/sulphamethoxazole versus placebo, trimethoprim/sulphamethoxazole versus no antibiotic treatment, furzolidone versus no antibiotic treatment and erythromycin compared to placebo

A trial conducted in South Africa [150] [EL = 1−] compared the effect of trimethoprim/sulphonamide to 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 do not specify which group received which treatment.

A second trial from South Africa [151] [EL = 1+] examined the effect of erythromycin compared to placebo for the treatment of non-specific gastroenteritis.

Children aged 1 m-2 years were included who had been admitted to 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 who received either erythromycin oral suspension, 40 mg/kg/day in divided doses for 5 days (*n* = 39), or placebo oral suspension (*n* = 39). Follow up was by daily examination for 7 days.

One trial conducted in Mexico [153] Rodriguez [EL = 1+] with three treatment arms compared the effects of furzolidone, trimethoprim/sulphamethoxazole and no antibiotic treatment for acute invasive diarrhoea in children.

Patients aged 2–59 m brought to hospital and seen in outpatients with three or more watery stools in previous 24 hours, up to 5 days diarrhoea prior to admission, and presence of PMN leukocytes and blood in stool (*n* = 125) were included in the study.

Following a complete physical examination and submission of a stool specimen participants were randomised to receive 7.5 mg/kg/day furazolidone in four equal doses a day for 5 days (*n* = 42), 8 mg/kg/day trimethoprim + 40/mg/kg/day sulphamethoxazole 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 sample 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 bacteriologic 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.

A second study from Mexico [152] [EL = 1−] recruited children aged 3–84 months seen in hospital with diarrhoea, into a treatment trial of trimethoprim/sulphamethoxazole against placebo.

Participants had passed three or more unformed stools in previous 24 hours, had <72 hours duration of diarrhoea, no antibiotic treatment in prior 7 days and were not severely dehydrated (*n* = 141) and were randomised into two treatment groups to receive 10 mg/kg/day trimethoprim + 50/mg/kg/day sulphamethoxazole oral suspension in two divided doses per 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 wks.

7.8.1 Trimethoprim/sulphonamide versus placebo

One trial [150] (*n* = 34) compared the effects of trimethoprim/sulphonamide with placebo and found no significant differences in the mean duration of diarrhoea (Group 1 = 5.250 +-3.118 versus Group 2 = 6.607 +-9.765), vomiting (Group 1 = 1.812 +-3.505 versus Group 2 = 1.607 +-2.998), pyrexia (Group 1 = 0.437 +-0.6549 versus Group 2 =0.642 +-0.9109) or in the duration of hospital stay (Group 1 = 156.687 +-93.672 versus Group 2 = 177.071 +-99.76) . [150]

7.8.2 Trimethoprim/sulphamethoxazole versus placebo

One study compared the effect of trimethoprim/sulphamethoxazole versus placebo

Outcome - Mean time to last diarrhoeal stool

The mean time to last diarrhoeal stool was significantly shorter with antibiotic use (compared to placebo) in all patients (58.2 versus 75.5 P = 0.021), those with fever (58.2 versus 75.5 P = 0.021) and those with faecal leucocytes (3>HPF)(57.7 versus 106.5 P = 0.025).

Outcome - Mean number of unformed stools

There was no significant difference between antibiotic and placebo groups in the mean number of unformed stools in 5 day period for all patients (9.8 versus 12.5) and those with fever (9.1 versus

17.3), although patients with 3>HPF who received antibiotics had significantly fewer unformed stools (10.1 versus 18.1 P = 0.041).

There was no significant difference in the number of unformed stools in wk 1 and wk 2 post treatment between the antibiotic and placebo group for all patients, patients with fever and patients with faecal leucocytes (3>HPF).

7.8.3 Erythromycin versus placebo

One trial [151] [EL = 1+] examined the effect of erythromycin compared to placebo for the treatment of non-specific gastroenteritis. The distribution of pathogens was similar between groups and results were presented for 32 antibiotic and 33 placebo recipients ..

There was no significant difference in the mean duration of abnormal stool frequency (WMD = -0.40 [95% CI -1.33 to 0.53]), vomiting (WMD = -0.30 [95% CI -0.93 to 0.33]), dehydration (WMD = 0.00 [95% CI -0.81 to 0.81]) or fever (WMD = 0.50 [95% CI -0.25 to 1.25]).

The erythromycin group had a significantly shorter mean duration of abnormal stool consistency compared to the placebo group (WMD = -0.80 [95% CI -1.46 to -0.14]). [EL = 1+]

7.8.4 Trimethoprim/sulphamethoxazole versus furzolidone versus no antibiotic treatment

One trial [153] [EL = 1+] with three treatment arms compared the effects of furzolidone, trimethoprim/sulphamethoxazole and no antibiotic treatment for acute invasive diarrhoea in children.

Outcome - Clinical cure by day 3

For furazolidone (RR = 1.93 [95% CI 1.21 to 3.09]), trimethoprim/sulphamethoxazole (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]), more participants who took antibiotics had been clinically cured by day 3 compared with the no antibiotics group.

Amongst those patients who had negative stool cultures, there was no significant difference in the proportion of patients who had been clinically cured at day 3, for either furazolidone (RR = 1.67 [95% CI 0.92 to 3.05]) or trimethoprim/sulphamethoxazole (RR = 1.57 [95% CI 0.85 to 2.87]) individually or for both antibiotics together (RR = 1.61 [95% CI 0.89 to 2.91]) compared with no antibiotic treatment

Outcome - Clinical cure by day 6

For furazolidone (RR = 2.78 [95% CI 1.25 to 6.19]), trimethoprim/sulphamethoxazole (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]), more participants who took antibiotics had been clinically cured by day 6 compared with the no antibiotics group.

Outcome - bacteriological cure at day 6

For patients with positive stool cultures, bacteriological cure at day 6 was only significantly different from placebo when data for antibiotics were combined (RR = 2.33 [95% CI 1.04 to 5.25]). No significant differences were found for furazolidone (RR = 1.76 [95% CI 0.76 to 4.12]) or trimethoprim/sulphamethoxazole (RR = 1.97 [95% CI 0.85 to 4.56]) alone compared to placebo.

Evidence summary

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 There was evidence from one small trial that the use of trimethoprim/sulphonamide in this way had no effect on duration of clinical symptoms (diarrhoea, vomiting or pyrexia) or on the length of hospital stay. [EL = 1−] Another trial found evidence that trimethoprim/sulphamethoxazole reduced the duration but not the severity of diarrhoea in the first 5 days of treatment. Antibiotic treatment only reduced severity of diarrhoea for children with increased faecal leukocytes and this protective effect was not seen by wk 1 or 2 post treatment. [EL = 1−] A third study found that erythromycin treatment reduced the mean duration of abnormal stool

consistency. [EL = 1+] A fourth trial reported that furazolidone and trimethoprim/sulphamethoxazole achieved a 'clinical cure' in all patients within three 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 was combined . [EL = 1+]

7.9 Traveller's diarrhoea

Evidence overview

No trials including children were identified, but a Cochrane systematic review of antibiotic treatment for travellers' diarrhoea in adults was included.[154] [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 to 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, ciprofoxacin (two trials), trimethoprim and trimethoprim-sulphamethoxazole, 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) to placebo (n = 264) were made in three trials and a significant reduction in the mean duration in diarrhoea was found in those receiving antibiotics (WMD -25.86 [95% CI -32.58 to -19.14]). 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= 27.989)

Six trials reported the number of patients cured at 72 hours. There were 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 (no. of unformed stools per 24 hour period) over 72 hours was reported by two trials. There was a small but 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]), 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 to 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

In patients with traveller's diarrhoea antibiotic treatment was effective in reducing the duration and severity of diarrhoea, although there was an increased incidence of side effects. [EL = 1+]

7.10 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.

7.10.1 *E. coli* 0157:H7

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

One prospective cohort study [155] 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* 0157:H7 were recruited to the study. Stool culture was obtained within first seven days of illness. On confirmation of *E. coli* 0157: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 (e.g., antibiotics, antimotility drugs). Prescription of medications was at the discretion of each physician and 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. Children were similar for demographic characteristics, clinical and laboratory outcomes at baseline. Overall 10/71 (14%) developed HUS. Nine children received antibiotics and five (56%) of these subsequently developed HUS. Of the 62 who did not receive antibiotics 5 (8%) developed HUS. This difference was 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 first 7 days after onset (RR= 17.3 [95%CI 2.2 to 137] p=0.007) and within first 3 days after onset (RR= 32.3 [95%CI 1.4 to 737] p= 0.03)). A significant linear trend was observed for initial white blood cell count and development of HUS (P=0.005). This remained significant after reanalysis as a continuous outcome and adjustment (RR = 1.5 [95%CI 1.1 to 2.1] p=0.02). A significant linear trend was also observed for the difference in HUS development according to the day stool culture was taken (P=0.01). This remained significant after adjustment (adjusted RR = 0.3 [95%CI 0.1 to 0.7] p=0.008).

A retrospective cohort study [156] also conducted in USA evaluated risk factors for progression of *E. coli* 0157:H7 to the development of HUS. [EL = 2+] Participants were <16 years old, resided in Washington State and either had symptomatic, culture proven *E. coli* 0157:H7 infection or had developed HUS in Jan-Feb 1993 (during an *E. coli* 0157:H7 outbreak from a 'fast food outlet' chain. Demographic, symptomatic and medication data was gathered from three sources: two telephone questionnaires administered to participants' parents (within 2 wks 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 outcome at baseline. The median age of participants was 6 years (range 0–15). 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 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 significant (RR= 2.0 [95%CI 0.5 to 7.7]) and (RR= 1.8 [95% CI 0.8 to 4.1]).

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 significant risk factor in this time interval (RR = 1.9 [95% CI 1.0–3.5]) 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 – 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 – 2.8]). Eight of these children went on to develop HUS compared to28/218 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 to 20/234 who received no antimotility treatments (p=0.10). There was no significant difference in the development of HUS in children who received adsorbant and antimotility drugs compared to those who did not (p=0.26)

There was no significant association 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/microL 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 WBC of over 13,000/microL 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* 0157: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 antimotility agents (with or without adsorbant agents) was associated with increased risk of HUS.

7.10.2 Salmonella

One retrospective review [157] 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 aged under one 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 7 had invasive complications (5 bacteraemia, 2 meningitis). Three risk factors were identified for the development of invasive salmonellosis. In total 45 (85%) of the 124 with non-invasive disease were aged below 6 months compared to 6 of the 7 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 5 of the 7 with invasive complications, but in only 25 of the 124 with non-invasive disease. One infant with bacteraemia died whilst awaiting a blood culture result. The authors suggested that empirical antibiotic treatment should given to infants under 6 months old who are febrile and dehydrated.

Another retrospective review [158] 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 mucoid stools compared with the rotavirus (p<0.0001) or non-specified (p<0.05) gastroenteritis groups. They were significantly younger (p<0.0001) than the rotavirus group and were less likely to have had at least one vomiting episode (p<0.01). Compared to the non-specified gastroenteritis group, the salmonella infected group had significantly longer stays in hospital (p<0.05), passed more stools per day (p<0.05) and more of them experienced fever during their admission (p<0.05). Additionally, patients with salmonella were significantly more likely to have been given antibiotics than both the rotavirus group (p<0.0001) and the non-specified group (p<0.05) although administration of antibiotics was not dependent on age. The salmonella group was also significantly more likely to have received IV fluids than the rotavirus group and to have received an antipyretic than the non-specified group (p=0.0002).

Evidence summary

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

Dehydration was 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 considered that gastroenteritis in children in the United Kingdom 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 might often be unnecessary. Antibiotic treatment carries with it a risk of adverse effects. Antibiotic therapy has itself been demonstrated to be a common cause of diarrhoea.

In most cases of childhood gastroenteritis the causative agent is not known. Stool microbiological investigations are performed in selected cases only (see Chapter X. Diagnosis). If a bacterial pathogen is identified using stool culture, the result would not be available at the time of presentation. The GDG considered the findings of studies from South Africa and Mexico in which antibiotic therapy was administered while awaiting the results of stool microbiological investigations. There was some evidence that in those local settings empirical treatment could have clinical benefits. The GDG considered, however, that such benefits were unlikely to be replicated in the UK where the spectrum of common pathogens is very different. The GDG concluded that routine administration of antibiotics should not be recommended.

Recommendations regarding the treatment of specific enteric pathogens were 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 were some individuals at increased risk of systemic sepsis. Young infants were at increased risk of developing salmonella gastroenteritis, and those under 6 months of age were at increased risk of systemic spread. Others likely to be at high risk of sepsis were 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 in patients with campylobacter spp. was 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 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 travellers' diarrhoea. The effect of antibiotic treatment for enteropathogenic and enteroinvasive *E. coli* was uncertain.

Only one study was available regarding antibiotic treatment for the protozoal pathogen *Cryptosporidium parvum*. This was somewhat unsatisfactory, but suggested possible benefit. Routine treatment was therefore not recommended, given that most cases could be expected to respond spontaneously.

Young children with *E. coli* 0157:H7 appeared to have a risk of 10–15% of developing haemolytic uraemic syndrome. There was evidence to suggest that those with a leucocytosis at presentation were at higher risk. Vomiting, especially in children under 5 years of age was also associated with an increase likelihood of progression to haemolytic uraemic syndrome. There was some evidence that antibiotic treatment might have been a risk factor for haemolytic uraemic syndrome though this finding was not consistent between studies. It might have been that this reported observation could 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* 0157:H7.

The GDG recognised that a number of other potential enteric pathogens existed 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 and *Entamoeba histolytica* 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, showing evidence of benefit from antibiotic treatment. It was therefore agreed that consideration should be given to 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 appropriate antibiotic treatment to the following:

- those with suspected septicaemia
- those with extra-intestinal metastatic bacterial infection
- infants under 6 months of age with salmonella gastroenteritis
- malnourished or immune deficient children (including HIV/AIDS) with salmonella gastroenteritis
- those with *Clostridium difficile*-associated pseudomembranous enterocolitis, dysenteric shigellosis, dysenteric amoebiasis, or cholera

Consider antibiotic therapy for those recently returned from overseas travel.

8 Other therapies

A range of other therapies have been proposed for use in gastroenteritis. These have focussed 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. probiotics.

A search was performed with no restrictions on date. From this, 1245 references were returned. The titles and abstracts of these were appraised for relevancy. From this, 163 papers were identified as relevant or potentially relevant to the guideline and were obtained in full-copy. .Of these, 33 were relevant and were included in this chapter which is divided into four sections. A further two papers were identified from updating searches [159],[160].

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 it 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 gastro-intestinal tract and it may be more effective than the phenothiazines for vomiting associated with gastroduodenal disease [161] 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 $5HT_3$ antagonists which block $5HT_3$ receptors in the gastro-intestinal 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 $5HT_3$ antagonist.

Evidence overview

Five trials were identified as relevant to this review [162],[163],[164], [159],[160]). Four of these were conducted in the US [163],[164],[159],[160] and one in Venezuela.[162] Two trials had three treatment arms [162],[160], the rest had two. Across the five studies, data from 639 children (aged 6 months to 12 years) suffering from gastroenteritis was collected.

The method of randomisation was reported in four studies.[163],[164],[159],[160] The outcome assessor was blinded in all studies. The proportion of patients randomised but lost to follow-up was reported in all

the studies (<20%). Four trials included a sample size power calculation.[163], [164], [159], [160] One study [160] was terminated early and reported findings for approximately half the number of expected participants (137/270). Comparability of the groups at study entry was adequate in three studies.[163], [164], [160] In one trial [162] it was only adequate on gender and food intake and in another [159] significantly more children in the ondansetron group were 'moderately' rather than 'mildly' dehydrated. Follow-up, treatment protocol and definition criteria for inclusion of the children with gastroenteritis varied between the three studies.

The following comparisons were investigated: oral ondansetron versus placebo, IV ondansetron versus placebo, IV metoclopramide versus placebo and IV dexamethasone versus placebo

The outcomes considered were duration of the disease (vomiting and diarrhoea outcomes), tolerance of ORT, need for intravenous fluid therapy, dehydration status and hospitalisation.

Oral Ondansetron versus placebo

Three RCTs [163], [164], [159] *n* = 466, compared the effects of the administration of oral ondansetron against the administration of placebo in children with GE. [EL = 1+] The participants were children aged between 6 months and 12 years that were treated in the emergency department for GE. The outcomes measured in these three RCTs were: cessation of vomiting in the first hours following the intervention, the need for iv rehydration, hospitalisation and diarrhoeal episodes during follow-up.

Outcome - cessation of vomiting

The data extracted from two trials [163], [164] was pooled in a meta-analysis. There was no evidence of statistical heterogeneity (I2=0%). Results showed that more children in the ondansetron groups stopped vomiting in the first few hours after treatment (146/181) compared to those who received placebo (116/178). This difference was statistically significant (RR=1.32 [95%CI 1.17 to 1.49]). (Fig 1)

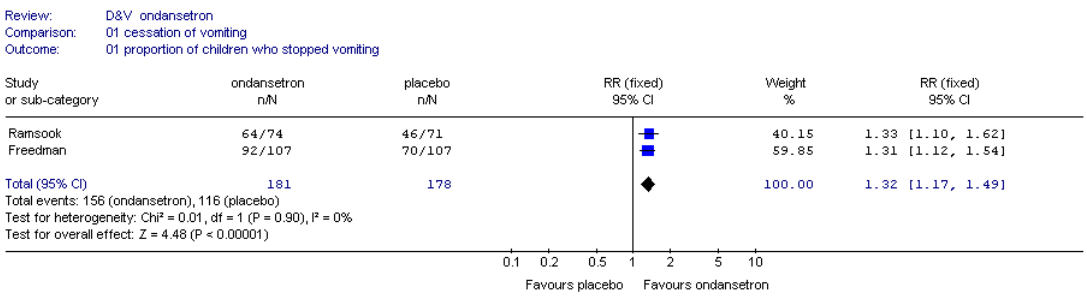


Figure 1

One RCT [159]reported that 93% of patients who had received ondansetron (*n* = 48) had had fewer than 3 episodes of vomiting during a 6 day follow up, compared to 88% in the placebo group (*n* = 48). [EL = 1+] Insufficient data was available to establish the statistical significance of this difference or of the reported mean number of vomiting episodes between the groups.

Outcome – use of intravenous fluid therapy

Three trials ([163], [164], [159]) 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 IV fluid therapy than those treated with placebo (79/233), the difference being statistically significant (RR=0.41[95%CI 0.28 to 0.59]), fig.2.

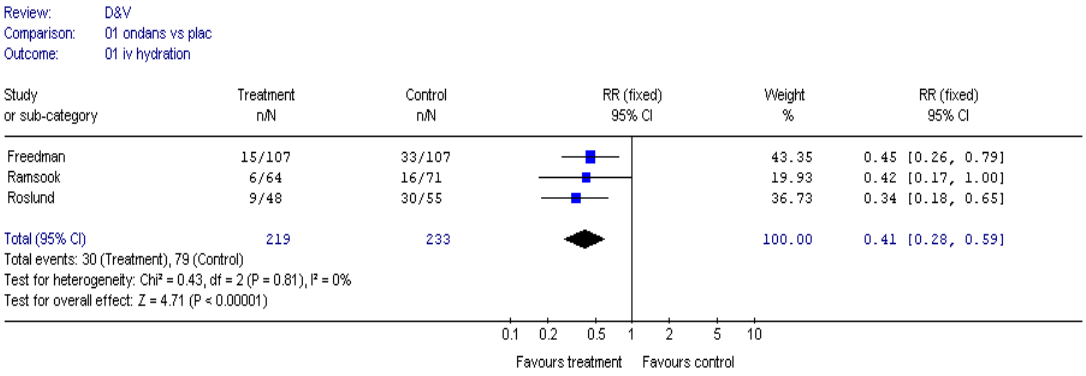


Figure 2

Outcome – admission to hospital

Three trials [163, 164, 159] reported the number of patients admitted to hospital after the Emergency Department stay. The data from the trials were pooled. The findings showed that significantly fewer children given ondansetron were admitted to hospital (9/232) compared to those given placebo (23/233) (RR=0.37[95%CI 0.15 to 0.92]) fig.3.

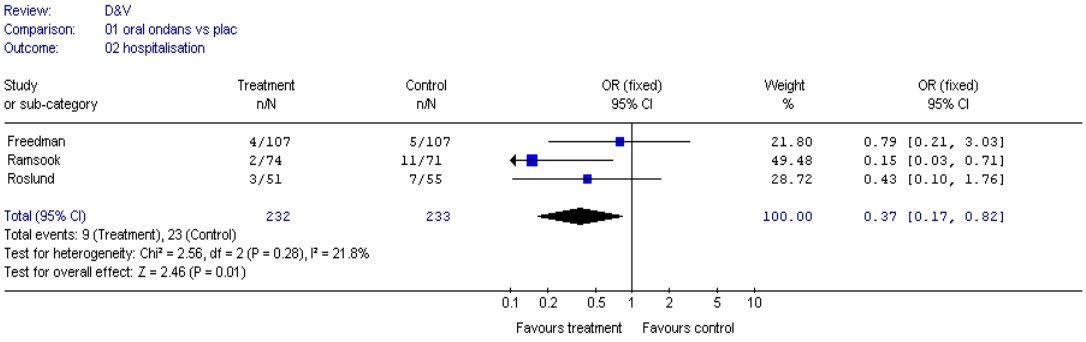


Figure 3

Outcome – number of episodes of diarrhoea

One RCT [163] found that the mean number of diarrhoeal episodes whilst undergoing rehydration (mean length of stay in emergency department 106 min ondansetron group versus 120 mins placebo group) was statistically significantly higher in children who had received ondansetron (mean 1.40) compared to the placebo group (mean 0.50) ($p< 0.001$) even after adjustment for number of episodes prior to admission.

A second RCT [164] similarly reported more episodes of diarrhoea whilst undergoing rehydration (mean length of stay in emergency department 2 hours ondansetron group versus 3 hours mins placebo group) in the ondansetron group (mean 0.70) when compared to the children receiving placebo, (mean 0.61), but the finding was not statistically significant (p=0.622). However, over the next 48 hours, children receiving ondansetron had 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 to 1.37 in the placebo group (n = 54) (p=0.002) and in the second 24 hours, 2.98 episodes (n = 62) compared to 0.96 episodes (n = 51) (p=0.015), respectively.

A third RCT [159] reported that 93% of patients who had received ondansetron (n = 48) had had fewer than 3 episodes of diarrhoea during a 6 day follow up, compared to 80% in the placebo group (n = 48). [EL = 1+] Insufficient data was available to establish the statistical significance of this difference or of the reported mean number of diarrhoeal episodes between the groups.

Intravenous ondansetron versus placebo

Two RCTs [162],[160] *n* = 173, each with three treatment arms, compared the effects of the administration of IV ondansetron with placebo in children suffering from GE. [EL = 1−] Participants were aged between 6 months and 12 years. The outcomes reported were: cessation of vomiting in the first 24 hours, number of episodes of diarrhoea, hospitalisation rates, oral hydration tolerance and dehydration status.

Outcome - cessation of vomiting first 24 hours

One RCT [162] found that 58% of the children receiving ondansetron had no emetic episodes in the first 24 hours after the administration of the drug, compared to 17% of the children receiving placebo). This difference was not statistically significant (RR= 3.50 [95% CI 0.91 to 13.53]).

Outcome – number of episodes of diarrhoea during the first 24 hours

In one RCT [162], 8 of 12 children receiving ondansetron had more than 4 episodes of diarrhoea while in the placebo group the number of children with more than 4 episodes of diarrhoea was 4 of 12. The difference was not statistically significant (RR=2.00 [95% 0.82 to 4.89])

Outcome – admission to hospital

One RCT [160] found that significantly more children who received placebo (9/44) required admission to hospital compared with those who had received ondansetron (2/46) (RR=0.21 [95%CI 0.05 to 0.93]).

Outcome - ORT tolerance

One RCT [160] found that more children who received ondansetron tolerated oral rehydration two hours after treatment (39/45) than those who received placebo (29/43). This difference was significant (RR = 1.28 [95% 1.02 to 1.68]). However, results taken at 4 hours post-treatment were statistically insignificant (IV ondansetron versus placebo = 9/14 versus 2/21, p=0.5).

Results for mean IV fluids administered and dehydration status were also similar between groups at 2 and 4 hours post-treatment.

Intravenous metoclopramide versus placebo

One RCT [162] *n* = 36, with three treatment arms, compared the effects of IV metoclopramide with placebo in children with gastroenteritis. [EL = 1−]

Outcome - cessation of vomiting first 24 hours

In the metoclopramide group 33% of the children had no emetic episodes for the first 24 hours, compared to 17% of the children receiving placebo. This difference was not statistically significant (RR=2.00 [95% CI 0.45 to 8.94])

Outcome - episodes of diarrhoea during the first 24 hours

10 out of 12 receiving metoclopramide had more than 4 episodes of diarrhoea while in the placebo group the number of children with more than 4 episodes of diarrhoea was 4 of 12. The difference was statistically significant (RR=2.50 [95%CI 1.08 to 5.79]).

Intravenous dexamethasone versus placebo

Outcome – admission to hospital

One study [160] found that there was no statistically significant difference in hospital admission rates for children who received placebo (9/44) compared to those who had received dexamethasone (7/47) RR = 0.29 [95% 0.07 to 1.15] . [EL = 1−]

Outcome - ORT tolerance

No significant difference in the numbers of children in each group tolerating oral rehydration was found at 2 or 4 hours - RR = 0.91 [95% 0.66 to 1.26] and IV dexamethasone versus placebo, 17/23

versus 12/21 p=0.5. Results for mean IV fluids administered and dehydration status were also similar between groups at 2 and 4 hours post-treatment.

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 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 intravenous fluid therapy 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 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 intravenous ondansetron, intravenous metoclopramide and intravenous 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 to children treated with placebo. The risk of having more than 4 diarrhoeal episodes was higher in both the treatment groups (intravenous ondansetron and intravenous metoclopramide group) compared to the placebo group, but the difference was statistically significant only for the intravenous 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 significant differences were found between intravenous dexamethasone and placebo groups for hospitalisation rates or oral rehydration therapy tolerance.

A simple economic model has also been developed (Appendix B) which demonstrates potential economic advantages of ondansetron, if given to children with persistent vomiting in whom IV fluids are being considered. However, further research is needed 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 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 controls 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, focussing particularly on the possible risk of worsened diarrhoea..

Research recommendation

A randomised controlled trial should be undertaken to further examine the safety of oral ondansetron for the management of persistent vomiting in children receiving ORT.

Why is this important?

Several randomised controlled trials have now shown that in children with persistent vomiting during ORT 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 that in the placebo groups. In one the number of stools passed during the rehydration phase was significantly greater, while 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 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 recurrence of dehydration or re-admission to hospital. If ondansetron is shown to both effective and safe in a secondary care setting then studies could also be undertaken to evaluate its use in primary care settings.

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, smectite) and charcoal have been employed. Antisecretory drugs such as racecadotril (a peripherally acting enkephalinase inhibitor) reduce intestinal water and electrolyte secretion. Bismuth subsalicylate 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 been advised that these medicines should 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

Two trials were identified as relevant to this review [165,166].

The larger trial (n = 97) was conducted in the Gambia [165] and compared the effect of kaolin with no treatment for diarrhoeal outcomes in children. The smaller trial (n = 39) conducted in Indonesia [166] compared the effect of activated charcoal with no treatment in children with acute gastroenteritis and severe dehydration. Both trials had two treatment arms. In total, data from 136 participants (aged 3 months to 10 years) was collected.

The method of randomisation was reported in both studies, but was inadequate in one study (birth order allocation)[165] and poorly reported in the other.[166] Allocation concealment and follow-up was not reported in either study. The treatment groups were slightly different in age and compliance with the doses of kaolin was poor in 33% of the participants of one study.[165] Method of randomisation, allocation concealment, follow-up, baseline comparability of the two groups was poorly reported in the [166] study.

Kaolin versus no treatment

A quasi-RCT was identified [165] that included children with diarrhoea aged between 3 and 18 months (n = 97). [EL = 1−] Those requiring antibiotic therapy or with positive diagnosis for malaria were excluded. Participants were allocated to treatment with kaolin and oral rehydration solution (n = 45) or to administration of oral rehydration solution alone (n = 52) by birth order. The outcomes considered were duration of diarrhoea and the number of stools per day in both groups**.**

Outcome - duration in days of the diarrhoeal episodes
No statistically significant difference was found in the mean duration of diarrhoeal episodes between the kaolin (mean 5.80 days, SD 4.70) and no treatment groups (mean 4.70 days, SD 4.30) (WMD=1.10[95%CI -0.70 to 2.90]).

Outcome - number of stools per day

There was no statistically significant difference in the mean number of stools per day between the children who received the adsorbent (mean 3.70, SD 1.20) and the children who did not receive it (mean 3.70, SD 1.00), (WMD=0.00 [95%CI -0.44 to 0.44]).

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 difference in the duration of acute diarrhoea and 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

Activated charcoal versus no treatment

One RCT was identified that included 39 children aged between 1½ months and 10 years old with acute gastroenteritis and severe dehydration.[166] [EL = 1−] Children with acute gastroenteritis due to *Entamoeba histolyca* were excluded. Participants were allocated to treatment with activated charcoal with oral and intravenous rehydration solution (n = 16) or oral and intravenous rehydration alone (n = 23). The outcomes considered were duration of diarrhoea and fluid therapy administered.

Outcome - duration of diarrhoea in days (mean)

The study found that the group receiving the activated charcoal had a significantly shorter mean duration of diarrhoea (mean 2.12, SD 0.80) than the control group (mean 3.00, SD 1.17), (WMD=-0.88 [95%CI -1.50 to -0.26]).

Outcome - total volume of ORES given

The study found that the activated charcoal group required significantly less oral rehydration solution (mean 3.25, SD 2.08) than the control group (mean 5.43, SD 3.22), (WMD=-2.18 [95%CI -3.84 to -0.52]).

Outcome - total iv fluids

The activated charcoal group required less IV fluid therapy with ringer lactate solution (n = 16 mean 3.19, SD 1.17) than the control group (n = 16 mean 3.74, SD 3.20), however, this difference was not statistically significant (WMD=0.55[95%CI -1.81 to 0.71]).

Evidence summary

There was some evidence from a poorly reported RCT [EL = 1+] 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 oral rehydration therapy required when compared with the standard rehydration therapy alone. On the other hand the same trial showed no difference in the amount of intravenous 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 to placebo or no treatment for diarrhoea in children was identified.[167] [EL = 1+]

This well-conducted systematic review included 9 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

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, the remaining three did not report such information. Participants were children aged between 1 to 60 months, inpatients and/ or out-patients. Definitions for the outcomes measures and the resolution of diarrhoea were different among the studies.

The methodological quality and conduction of the studies was 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 an intention-to-treat analysis was considered. All the trials had >80% of follow-up.

Smectite versus placebo or versus no treatment

Data was extracted for the following outcomes: duration of diarrhoea, frequency of stools, vomiting and adverse events. The review reported also the proportion of patients without diarrhoea by day 3 and five as well as the proportion of those presenting diarrhoea for more than seven days.

Outcome - duration of diarrhoea (hours)
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 [95%CI -24.80 to -20.61]).

Outcome - frequency of stools
Two studies provided data on the number of stools. The two trials were pooled together. No statistically significance difference was found between the intervention and the control group in the number of stools and for the first 24 hours of follow-up: at 6 hours (WMD=-0.07 [95%CI -0.6 to 0.4]) and from the first 6 hours to the first 24 hours (WMD=-0.33[95%CI -0.8 to 0.2]). However, it did show that children treated with smectite had a significant reduction in the number of stools from the first 24 hours period onwards: at 24 to 48 hours (WMD=-0.62 [95%CI -1 to -0.2]), and at 48 to 72 hours (WMD=-0.58 [95%CI -0.9 to -0.3]).

Outcome - resolution of diarrhoea by day 3 and by 5
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 significantly higher than the proportion of children that were not treated with smectite, (RR=1.64 [95%CI 1.36 to 31.98]). By day 5, using a random effect model, the difference was not significant (RR=1.19 [95%CI 0.93 to 1.53]).

Outcome - diarrhoea for > 7 days
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=0.6 [95%CI 0.42 to 0.85]).

Outcome – vomiting frequency (number of episodes)
The results of two studies that reported the number of episodes of vomiting were combined. No significant difference in the number of vomiting episodes between the two groups was found, (WMD=-0.02 [95%CI -0.5 to 0.6]).

Outcome - duration of vomiting (hours) and incidence of vomiting
One RCT reported the duration of vomiting and showed no statistically significant difference between the children receiving smectite and the ones that did not receive the drug, (WMD=-0.1 [95%CI -0.15 to 0.3]).

Another trial compared the effects of administering smectite in the incidence of vomiting in day 1 and in day 3 of the intervention: no significant difference was found, (RR=1.0 [95%CI 0.9 to 1.2]) and (RR= 1.2 [95%CI 0.9 to 1.4]).

Adverse Events

Two trials reported a higher incidence of constipation among the children in the intervention group but the difference, when compared with the control group children was not statistically significant (RR=5.8 [95%CI 0.7 to 47.1]).

* 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 seven days. On the other hand the review showed no difference between the smectite group and the control group in the number of episodes and duration of vomiting and in the resolution of diarrhoea by day 5. 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 and three trials of bismuth subsalicylate were identified.

Two trials compared the effect of racecadotril to placebo.[168],[169] One trial (*n* = 135) conducted in Peru [168] recruited boys admitted to hospital for dehydration. The second trial (*n* = 172) conducted in France [169] had participants of both sexes hospitalised for severe acute diarrhoea. Both trials had two treatment arms. In total, data from 307 participants (aged 3 months to 4 years) was collected.

There was no detail provided about sequence generation, allocation concealment or blinding of assessors in either study, however groups were broadly comparable at baseline in both trials. 17% of all participants were lost to follow up in one study [168] although there were considerable losses in data collection and follow up (28%) in the other.[169] The latter presented both full data set (*n* = 168) and per-protocol results (*n* = 121). Only per-protocol results were reported here but these were not clearly presented and most outcome measurements were estimated from graphs.

Three RCTs investigating bismuth subsalicylate were identified from the searches [170],[171] 1991. One was conducted in Bangladesh [170], one in Peru ([171] and one in Chile.[172] Two trials had two treatment arms [170],[172], the third had three. Across the three trials, data from 808 children was collected.

These were three well-conducted double-blind placebo-controlled randomised trials. The method of randomisation was not reported in one study [172], however, the allocation concealment, the loss to follow-up (<20%) and the baseline comparability of the two groups were adequate for all the three studies. 'Intention to treat' analysis was not performed in any of the three trials

8.2.2.1 Racecadotril

Racedotril versus placebo

One RCT [168] (*n* = 135) examined the effect of racecadotril compared to placebo in boys aged between 3–35 months admitted to hospital for dehydration. [EL = 1+] Included participants had passed watery diarrhoea for 5 days or less, had passed 3 or more diarrhoeic stools in 24 hours prior to admission and had passed 1 diarrhoeic stool within 4–6 hours post-admission. Racecadotril (1.5 mg/kg body weight) (*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. Recorded outcomes included stool output, duration of diarrhoea and overall cure rate measured at 5 days.

A multicentre RCT [169] (*n* = 172), conducted in 13 centres in France, examined the effect of racecadotril compared to placebo in children of both sexes aged between 3 m to 4 years hospitalised for severe acute diarrhoea. [EL = 1−] Included participants had passed watery diarrhoea (3 watery

stools/day or more) for less than 72 hours duration and had passed one watery stool post-admission to hospital. Racecadotril (1.5 mg/kg body weight) (*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. Treatment given for 5 days or until diarrhoea stopped. Four measures of stool output were presented.

Outcome - mean stool output in first 48 hours

One trial [168] reported a significant difference in the mean 48 hour stool output favouring racecadotril over placebo for all participants and for both the rotavirus positive and negative groups. [EL = 1+]

For all participants (*n* = 135), the mean stool output was 92 +/- 12 g/kg in the racecadotril group (*n* = 68) compared to 170 +/- 15 g/kg in the placebo group (*n* = 67). This reduction was statistically significant (P<0.001).

A 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 was 105 +/- 17 g/kg and 195 +/- 20 g/kg in the placebo group (*n* = 39) (P<0.001). The authors state that in the rotavirus negative subgroup (*n* = 62), there was a significant reduction in the mean 48 hour stool output in participants receiving racecadotril compared to those receiving placebo (31% lower in the racecadotril group [95%CI 16%-46%] p<0.001).

Outcome - hourly stool output in first 24 hours

One trial [169] reported the mean hourly rate of stool production in first 24 hours. This was found to be lower in the racecadotril group (*n* = 58) (11 g/hour) compared to the placebo group (16 g/hour). 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) [EL = 1−]

Outcome – hourly stool output in first 48 hours

Two trials reported consistent results on the hourly rate of stool production in first 48 hours.

In the first trial [168], for all participants (*n* = 135), the mean hourly rate of stool production in first 48 hours was statistically significantly lower in the racecadotril group (*n* = 68) (1.8 +/- 0.2 g/kg/hour) compared to the placebo group (*n* = 67) (3.1 +/- 0.3 g/kg/hour) (P<0.001) [EL = 1+]

Using covariate analysis, the mean hourly rate of stool production in first 48 hours was found to be statistically significantly lower in the racecadotril group (*n* = 53) (8 g/hour) compared to the placebo group (*n* = 63) (16 g/hour) (P<0.001) in the second trial.[169] The authors estimated that this indicated a treatment difference of a 50% reduction in stool output [95% CI 33% to 75%][EL = 1−]

The authors stated that this effect was independent of rotavirus status (covariate analysis: rotavirus X treatment interaction p=0.5) and that racecadotril was similarly significantly effective in the rotavirus positive (8 g/hour versus placebo 19 g/hour) and negative (6 g/hour versus placebo 13 g/hour) groups (p=0.001)

Outcome - mean total stool output before recovery

One trial [168] reported that for all participants, the mean total stool output before recovery was 157+/- 27 g/kg in the racecadotril group (*n* = 68) compared to 331 +/-39 g/kg in the placebo group (*n* = 67). This reduction was statistically significant (P<0.001). [EL = 1+]

A significant reduction in mean stool output before recovery 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 397+/-37 g/kg in the placebo group (*n* = 39) (P<0.001). Although no further details are provided, the authors stated that in the rotavirus negative subgroup (*n* = 62), there was a significant reduction in the mean stool output before recovery in participants receiving racecadotril compared to those receiving placebo (37% lower in the racecadotril group [95%CI 20%-56%] p<0.001).

Outcome - duration of diarrhoea

One trial [168] reported that the median duration of diarrhoea was less 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 to 52 hours in the rotavirus negative participants

Outcome – 'cure rate' at 5 days

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 to 44 cured participants in the placebo group. This difference was statistically significant (RR = 1.28 [95% CI 1.04 to 1.56] p=0.02)

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 body weight 3 times daily) and oral rehydration had a reduced total and average hourly stool output 48 hours after starting treatment compared to children given placebo and oral rehydration. The effect on total stool output was independent of rotavirus status. Another 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

Bismuth subsalicylate versus placebo

Three RCTs comparing the effects of bismuth subsalicylate (BSS) to placebo were identified.

The largest RCT[170], n = 451, compared the effects of administering BSS (100 mg/kg per day) to children presenting with acute diarrhoea against the administration of placebo. [EL = 1+] Participants were children aged between 4 and 36 months with a history of acute watery diarrhoea.

The second RCT [172], n = 142, examined the effects of treating children aged between 4 to 36 months and suffering from diarrhoea and dehydration with bismuth subsalicylate. [EL = 1+] The study compared the effects of administering BSS (100 mg/kg) for 5 days against placebo.

A RCT with three treatment arms[171], n = 215, compared the effects of administering BSS to treat diarrhoea with placebo. [EL = 1+] Participants were boys between 6 to 59 months that had three or more watery stools in the preceding 24 hours. Children were randomised to treatment with BSS 100 mg/kg, BSS 150 mg/kg or placebo.

The outcomes considered varied across the three studies and these were: 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.

Outcome - onset persistent diarrhoea

The [170] study found that the proportion of children who developed persistent diarrhoea was 8% among those treated with BSS and 11% among those receiving placebo. This finding was not statistically significant, (RR 0.71 [95%CI 0.39 to 1.28])

Outcome - duration of diarrhoea

Three trials presented findings for this outcome.

In one trial [170] children receiving bismuth had a shorter duration of the acute diarrhoea (median 36 hours) when compared with the children who received placebo (median 42 hours). The finding was not statistically significant, p=0.057. When considering those children positive to rotavirus, the authors found a significant reduction in the duration of diarrhoea among the children treated with

bismuth (median 56 hours) when compared to the children receiving placebo (median 72 hours), p=0.03.

Another study [172] found that 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). The authors reported that this difference was statistically significant, p<0.02. The mean time until last unformed stool was also shorter in the group treated with BSS (mean: 130.4 hours) compared with the group receiving placebo (mean: 107.5). The difference between the two groups was reported as statistically significant, p<0.01.

In the third trial[171], diarrhoea stopped within the fifth day of admission in 76/85 (89%) children treated with 100 mg/kg BSS, 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 significantly more children in each of the two intervention groups compared to the control group (100 mg/kg BSS versus control RR = 1.21 [95%CI 1.05 to 1.40] and 150 mg/kg BSS versus control RR = 1.19 [95% CI 1.03 to 1.38]).

Outcome - total output (stool+urine)

One study [170] reported a statistically significant difference between the intervention group and the group receiving placebo. Children treated with bismuth had a lower output of stool and urine (mean 386.00 g/kg, SD 248.00) than the children receiving placebo (mean 438.00 g/kg, SD 272.00), (WMD -52.0 [95%CI -100.05 to -3.95]).

Outcome - mean total stool output (ml/kg)

In a RCT with three treatment arms[171], the mean total stool output was 182 ml/kg (SD 197) in children treated with 100 mg/kg BSS (*n* = 85), 174 ml/kg (SD 159) children treated with 150 mg/kg BSS (*n* = 83) and 260 ml/kg (SD 254) in children receiving placebo (*n* = 84). The mean total stool output was significantly reduced in each of the two intervention groups compared to the control group (100 mg/kg BSS versus control, WMD = -78.00 [95%CI –146.59 to –9.41] and 150 mg/kg BSS versus control, WMD = -86.00 [95% CI –150.19 to –21.81]).

Outcome - total volume of vomitus (ml/kg)

The same three armed study presented findings for emesis[171]. The mean total volume of vomitus was 11.60 ml/kg (SD 19.60) in children treated with 100 mg/kg BSS (*n* = 85), 8,70 ml/kg (SD 18.30) children treated with 150 mg/kg BSS (*n* = 83) and 16.20 ml/kg (SD 27.00) in children receiving placebo (*n* = 84). The mean total volume of vomitus was significantly reduced in the group receiving 150 mg/kg BSS compared to the control group (WMD = -7.5 [95% CI –14.49 to –0.51]). No statistically significant difference in effect was found between the group receiving 100 mg/kg BSS and the placebo group (WMD = -4.60 [95%CI –11.72 to 2.52]).

Outcome - fluid intake (ml/kg)

Three studies presented findings on fluid intake[172,171]. One used the mean total intravenous fluid intake as an estimate[172], one used the mean total intake of oral rehydration solution [170] and one used the mean total IV and oral intake of rehydration solutions [171]

One trial [172] showed that 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 an histogram and therefore these 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 in the control group 42 ml/kg

In one study [170], the mean of the total intake of oral rehydration solution was 386 ml/kg in the intervention group and 291 ml/kg in the control group. The difference found between the two groups was not statistically significant, (WMD-34.0 [95%CI -70.99 to 2.99]).

In the three armed trial[171], the mean total intake of rehydration solutions was 239 ml/kg (SD 177) in children treated with 100 mg/kg BSS (*n* = 85), 236 ml/kg (SD 152) children treated with 150 mg/kg BSS (*n* = 83) and 314 ml/kg (SD 234) in children receiving placebo (*n* = 84). The mean total intake of rehydration solutions was significantly reduced in each of the two intervention groups compared to

the control group (100 mg/kg BSS versus control, WMD = -75.00 [95%CI –137.61 to –12.39] and 150 mg/kg BSS versus control, WMD = -78.00 [95% CI –137.78 to –18.22]).

Outcome - duration of hospital stay (days)

Two studies provided data on the duration in hospital stay [172,171]).

One study [172] found a statistically significant reduction in the duration of hospitalisation among the group treated with BSS when compared to the group receiving placebo. The mean of hospital stay for the intervention group was 6.9 days, while for the control group was 8.5, p=0.01.

One study[171] found that the mean length of hospital stay was 3.3 days (SD 1.5) in children treated with 100 mg/kg BSS (*n* = 85), 4.1 days (SD 2.1) children treated with 150 mg/kg BSS (*n* = 83) and 3.4 days (SD 1.5) in children receiving placebo (*n* = 84). The mean length of hospital stay was significantly reduced in each of the two intervention groups compared to the control group (100 mg/kg BSS versus control, WMD = -8.00 [95%CI –1.35 to –0.25] and 150 mg/kg BSS versus control, WMD = -0.70 [95% CI –1.25 to –0.15]).

Adverse events

No adverse reactions were observed during the three trials. It was reported that two children had 'black tongue' during treatment in one trial [170].

Bismuth subsalicylate (100 mg/kg/d) versus bismuth subsalicylate (150 mg/kg/d)

One RCT with three treatment arms [171], *n* = 215, compared the effects of administering BSS 100 mg/kg versus BSS 150 mg/kg to treat diarrhoea. [EL = 1+] Participants were boys between 6 to 59 months that had three or more watery stools in the preceding 24 hours. The outcomes of interest were: duration of diarrhoea, total stool output, total volume of vomitus, total intake of rehydration and duration of hospitalisation.

Outcome - duration of diarrhoea (proportion of children with diarrhoea by day 5)

Diarrhoea stopped within the fifth day of admission in 76/85 (89%) children treated with 100 mg/kg BSS, 73/83 (88%) children treated with 150 mg/kg BSS. No statistically significant difference in effect was found between the two intervention groups (RR = 1.02 [95%CI 0.91 to 1.13]).

Outcome - mean total stool output (ml/kg)

The mean total stool output was 182 mL/kg (SD 197) in children treated with 100 mg/kg BSS (*n* = 85) and 174 ml/kg (SD 159) children treated with 150 mg/kg BSS (*n* = 83). No statistically significant difference in effect was found between the two intervention groups (WMD = 8.00 [95%CI –46.07 to 62.07]).

Outcome - total volume of vomitus (ml/kg)

The mean total volume of vomitus was 11.60 ml/kg (SD 19.60) in children treated with 100 mg/kg BSS (*n* = 85),and was 8.70 ml/kg (SD 18.30) children treated with 150 mg/kg BSS (*n* = 83). No statistically significant difference in effect was found between the two intervention groups (WMD = 2.90 [95%CI –2.03 to 8.63]).

Outcome - mean total intake of rehydration -oral and iv fluids (ml/kg)

The mean total intake of rehydration solutions was 239 ml/kg (SD 177) in children treated with 100 mg/kg BSS (*n* = 85) and 236 ml/kg (SD 152) children treated with 150 mg/kg BSS (*n* = 83). No statistically significant difference in effect was found between the two intervention groups (WMD = 8.00 [95%CI –46.07 to 62.07]).

Outcome - duration of hospital stay

The mean length of hospital stay was 3.3 days (SD 1.5) in children treated with 100 mg/kg BSS (*n* = 85) and 4.1 days (SD 2.1) children treated with 150 mg/kg BSS (*n* = 83). No statistically significant difference in effect was found between the two intervention groups (WMD = -0.10 [95%CI –0.55 to 0.35]).

Adverse events

The authors were mainly interested in recording adverse reactions concerning the potential neurotoxic effects of the drug. However, none of the children treated with BSS had adverse reactions.

Evidence summary

Three RCTs with EL 1+ were identified for the effectiveness of bismuth subsalicylate 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 bismuth subsalicylate with oral rehydration solution had a reduction in the duration of diarrhoea, in the duration of hospital stay and in the need for fluid therapy. However results from the third RCT, which had a large sample size, did not show a reduction in the duration of diarrhoea, in the incidence of persistent diarrhoea, or in the total intake of oral rehydration solution in the group of children treated with bismuth subsalicylate compared to the placebo group. In this trial, a 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 outputs and one trial showed a statistically significant reduction in vomiting patients receiving a higher dose of bismuth. No evidence of benefit was found between the administration per day of 100 mg/kg versus 150 mg/kg of bismuth subsalicylate in the treatment of diarrhoea in children for this outcome or any other outcome estimated. No adverse events were identified although two incidences 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 to placebo for diarrhoea in children was identified.[173] [EL = 1+] This well-conducted systematic review included 13 RCTS published between 1980 and 1999. From the 13 studies four 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 > 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 (even if in most of the trials participants were mildly dehydrated and had diarrhoea for less than 3 days prior inclusion in the studies).

8.2.3.1 Loperamide

Loperamide versus placebo

Data was extracted and meta-analysis was performed for the following outcomes: diarrhoea continuing at 24 hours and 48 hours, reduction in diarrhoea duration, diarrhoea counts for the first 24 hours and adverse events.

Outcome - diarrhoea at 24 hours

In the four trials reporting diarrhoea at 24 hours, the prevalence of diarrhoea among the group treated with loperamide was 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 similar, (RR=0.66 [95%CI 0.56 to 0.77]).

Outcome - diarrhoea at 48 hours

Data on the proportion of patients with diarrhoea at 48 hours was available in four studies. The meta-analysis performed showed that the loperamide group had a significantly higher proportion of patients without diarrhoea when compared to the control group, (RR=0.59 [95%CI 0.45 to 0.78]).

Outcome - duration diarrhoea (mean +- SD)

The mean duration of diarrhoea was obtained combining the data from six trials. It was found that the group receiving loperamide had a shorter duration of diarrhoea in days when compared to the control group, (WMD=-0.80 [95%CI -0.87 to -0.74]). When restricting the analysis to those five studies administering a loperamide dose of <= 0.25 ml/kg/d, the result was similar, (WMD=-0.7 [95%CI -0.6 to -0.8]).

Outcome - stool count at 24 hours (mean +- SD)

Four studies were included in the meta-analysis for the number of stools at 24 hours. The group treated with loperamide showed a lower mean number of stools than the control group, (count ratio=0.84 [95%CI 0.77 to 0.92]).

Adverse events

Twelve RCTs reported information on serious adverse events. Those were defined as presence of ileus, lethargy or death. When pooling the data together it was found that 8 participants out of 927 in the intervention group and 0 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 4 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 to children that did not receive the drug. Serious adverse events only occurred in the children receiving loperamide and these participants also had significantly more 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 if there is treatment available to alleviate it. Various antidiarrhoeal agents have been proposed and some have been widely used. However, most authorities now advise the avoidance of antidiarrhoeal medications. They have been considered relatively ineffective, unnecessary and potentially harmful.

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

The GDG 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 was required to examine the possible clinical and health economic benefits that might be associated with its use in the UK. Studies on bismuth subsalicylate 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 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

Further studies should be undertaken to examine the effectiveness and safety of racecadotril (an enkephalinase inhibitor), and also smectite (a clay mineral) as antidiarrhoeal agents.

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.[174] In developing countries, zinc deficiency may be common due to inadequate food intake, reduced availability in animal food sources, and high phytate content in the diet resulting in impaired absorption.[175] In 1995 a study from India first reported significant clinical benefit from zinc therapy in gastroenteritis[176]. 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 which acts as important substrate for rapidly dividing cells, including enterocytes and lymphocytes. It has therefore been postulated that glutamine supplementation might be of benefit in gastroenteritis.[177] 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[178]. 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 review was identified that included 18 trials in total (Lazzerini 2008). Eight of these trials were relevant here [179,180,174,181,182,183,176,184]), the remainder being excluded as participants were malnourished or had persistent diarrhoea.

Three of the studies were conducted in India [180,183,176], two in Bangladesh [182,174] one in Brazil [179] and one in Nepal.[184] The remaining study was a multi-centre trial carried out in Pakistan, India and Ethiopia ([181]). Seven studies had two treatment arms and one had three arms.[174] Across the eight studies 5155 participants suffering from acute diarrhoea (children aged from one to 60 months) were enrolled. Trials enrolling exclusively malnourished children were not included in this review. Four studies were hospital-based trials [179,180,183] three were community-based trials [181,176,184] and one study included outpatient participants as well as inpatient.[182]

All of the eight trials included in this review were RCTs. In one study the method used to generate the allocation sequence was unclear [183], in the other seven trials the method of randomisation was considered adequate. Five studies assured adequate allocation concealment [180,181,182,176,184]; in the remaining three this was unclear.[174,183] The outcome assessor was blinded in seven trials and unclear in one.[183] Only five trials reported a sample size power calculation.[180,174,181,182,176] 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.[183] 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.

Zinc versus placebo

Six trials administered zinc alone [179,180,174,181,182,183,176,184] and two trials administered zinc with a multivitamin preparation.[180,176] In one trial [179] the placebo group received vitamin C while the intervention group did not. The outcomes measured were duration of diarrhoea, stool output, hospitalisation, death and adverse events (vomiting). Not all the studies that had been included reported all the outcomes.

One RCT[179] *n* = 81, was aimed at determining the effect of oral zinc supplementation on the duration of acute diarrhoea in young children. [EL = 1−] Participants were children 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 five days or until resolution of diarrhoea.

An RCT [180] *n* = 287, examined the clinical benefit of zinc supplementation as an adjunct to oral rehydration therapy on stool output and duration of diarrhoea in children with non-cholera diarrhoea. [EL = 1+] Participants were outpatients aged between 3 and 36 months old, with diarrhoea for less than 72 hours and mild dehydration.

Another RCT [174] *n* = 275, 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 children with acute diarrhoea. [EL = 1+] Participants were male children aged between 1 and 6 months, hospitalised and with diarrhoea for less than 3 days.

A multi-centred randomised controlled trial [181] *n* = 1110, assessed safety and therapeutic effects of supplementing with zinc children suffering from diarrhoea. [EL = 1+] It compared the impact of administering 10 mg of zinc sulfate per day for 14 days against placebo for the treatment of acute diarrhoea. Participants were outpatients, aged from 1 to 5 months.

One RCT [182] *n* = 1067, was aimed to determine if daily zinc supplementation was associated with an increase risk of vomiting in children with diarrhoea. [EL = 1+] The study compared 20 mg of zinc supplementation per day for 10 days against placebo. Participants were young children aged between 3 and 59 months with diarrhoea and admitted in hospital or in the outpatient clinic.

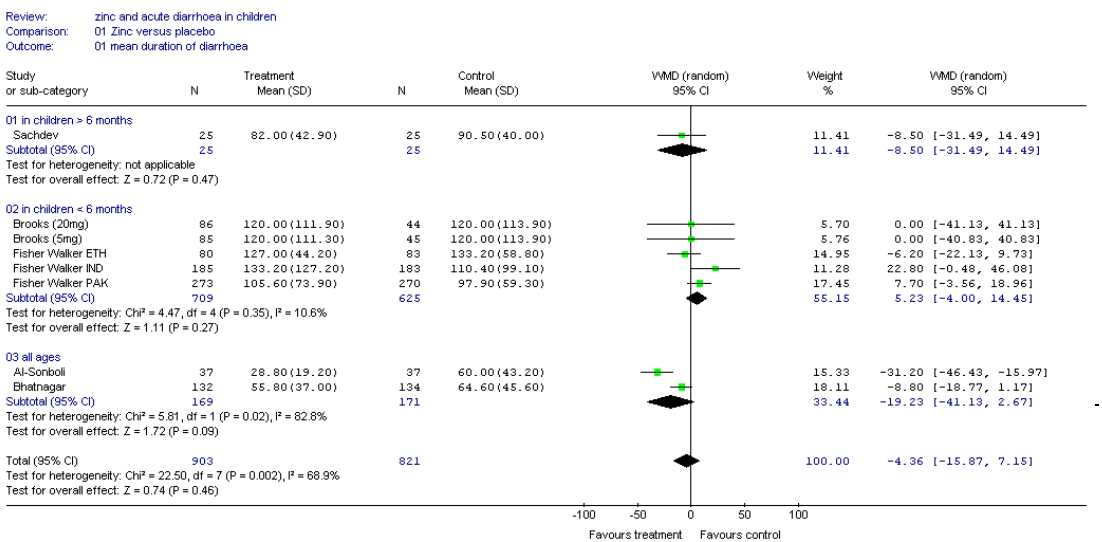
An RCT [183] *n* = 50, assessed the impact of zinc supplementation on the duration of diarrhoea and stool frequency in children with acute dehydrating diarrhoea. [EL = 1−] It compared the administration of 40 mg of elemental zinc against the administration of placebo in children aged from 6 to 18 months. Participants were hospitalised and followed until recovery.

An RCT [176] *n* = 947, was aimed to evaluate the effects of daily supplementation with 20 mg of elemental zinc on the severity of acute diarrhoea. [EL = 1+] The study compared the administration of zinc with the administration of placebo. Participants were children from 6 to 35 months and who had diarrhoea for less than 7 days. All participants enrolled received multivitamin supplementation.

Another study [184] *n* = 899, was designed to measure the impact of daily zinc supplementation on the duration and severity of acute diarrhoea in children. [EL = 1+] The trial did also assessed the effect of administering zinc with vitamin A but only the zinc supplemented group and the placebo group have been considered. Participants were children between 6 and 35 months that presented with diarrhoea for less than 96 hours.

Outcome - mean duration of the diarrhoea (hours)

Five trials reported the mean duration of diarrhoea. The results of these are presented trials according



Diarrhoea a

to participants' age in figure 1 below. One small trial [179] reported a significant reduction in the mean duration of diarrhoea for children given zinc compared to those given placebo (WMD= -31.20 [95%CI -46.43 to -15.97]). Meta-analysis of all five trials results found no statistically significant difference in mean duration of diarrhoea between those receiving zinc (*n* = 903) or placebo (*n* = 821), (significant heterogeneity found (I2 >50%), therefore the random effects model was used. WMD= -4.36 [95%CI -15.87 to 7.15]).

Figure 4

Outcome - proportion of children with diarrhoea by day 3

Only one trial (*n* = 891)[184] reported the proportion of children with diarrhoea by the 3rd day of follow-up. It showed a statistically significant difference favouring the group that received the zinc supplementation (27% children with diarrhoea) when compared to the group receiving the placebo (35% children with diarrhoea), (RR=0.75 [95%CI 0.62 to 0.92]).

Outcome - proportion of children with diarrhoea by day 5

The proportion of children with diarrhoea by the 5th day from the start of the study was measured in one trial (*n* = 266)[180]. The findings showed that more children were still suffering from diarrhoea in the placebo group (27/134) compared with the intervention group (17/132) but the difference was not statistically significant, (RR=0.64 [95%CI 0.37 to 1.12]).

Outcome - proportion of children with diarrhoea by day 7

Data from four studies (*n* = 3168) were combined in a meta-analysis (I2>70%) that showed no statistically significant difference between the two groups in the proportion of children with diarrhoea by day 7, (RR=0.90 [95%CI 0.64 to 1.27]).

Four trials (*n* = 3168) reported the proportion of children with diarrhoea by day 7. Results are presented according to participants' age in figure 2 below. Two trials [184],[180] reported that significantly fewer children given zinc had diarrhoea by day 7 compared to those given placebo. The first reported this finding in children between 6 and 35 months of age (RR=0.58 [95%CI 0.38 to 0.87]), the second in children aged between 3 and 36 months of age (RR=0.11 [95%CI 0.01 to 0.88]).

Meta-analysis of the results of the four trials found no statistically significant difference in the proportion of children with diarrhoea by day 7 between those receiving zinc (*n* = 1568) or placebo (*n* = 1600), (significant heterogeneity found (I2 >50%), therefore the random effects model was used. RR=0.90 [95%CI 0.64 to 1.27]).

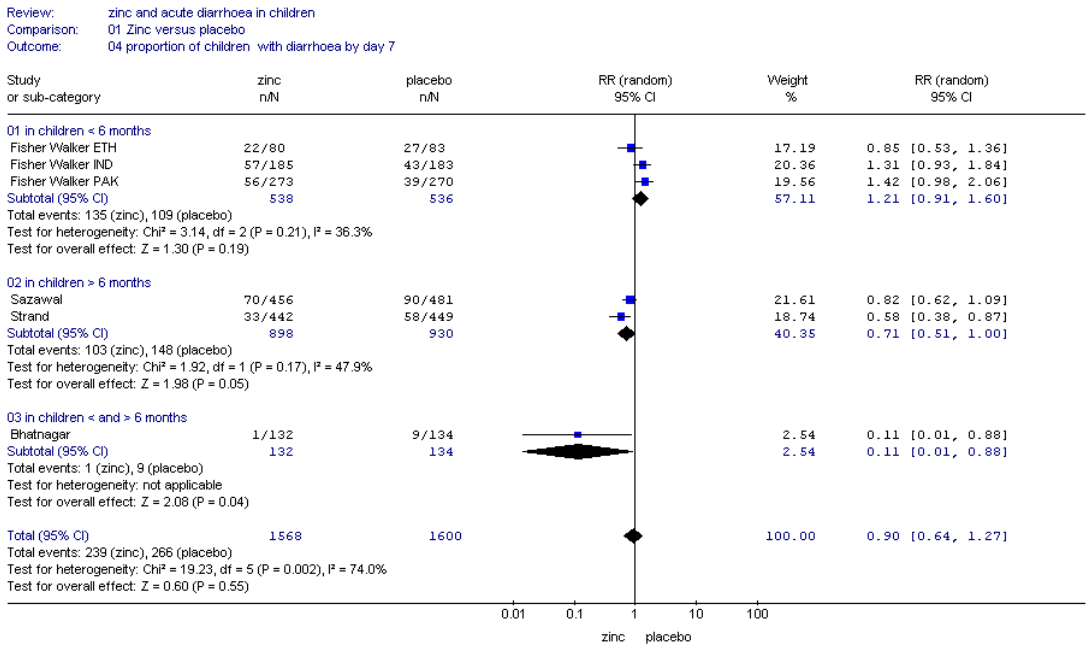


Figure 5

Outcome - stool frequency (number stools/day)

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 3 below. Two trials [176],[179] reported that children given zinc had significantly lower stool frequency than those given placebo. The first trial made this finding in children aged between 6 and 35 months of age (WMD=-2.00 [95%CI -3.61 to -0.39]), the second in children aged between 3 and 36 months of age (WMD=-5.20 [95%CI -8.52 to-1.88]).

Meta-analysis of the results of the four trials found no statistically significant difference in stool frequency overall between those receiving zinc (*n* = 1056) or placebo (*n* = 1079), (significant heterogeneity found (I2 >50%), therefore the random effects model was used. (WMD=-0.32 [95%CI -0.8 to 0.17]). There was a significant reduction in stool frequency for children aged over 6 months given zinc, compared to placebo (2 RCTs), (WMD=-1.90 [95%CI -3.22 to -0.58])

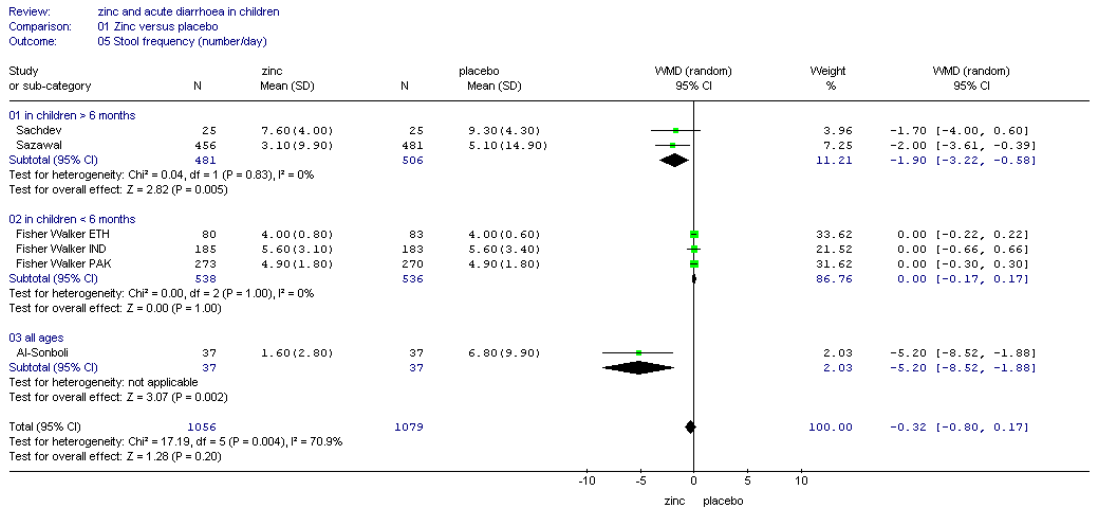


Figure 6

Two trials reported the geometric mean number of stools per day. One study [174] which recruited only infants of less than 6 months of age, reported the geometric mean and confidence intervals for this outcome. The authors found no statistically significant differences between the three groups: The geometric mean of the number of diarrhoeic stools was 5 (5, 6) for the group receiving 5 mg of zinc, for the group receiving the higher dose of zinc -20 mg- as well as for the placebo group. One study [184], which included children aged from 6 to 35 months, measured the geometric mean of the number of stools in the first 4 days of follow-up. When comparing the intervention group against the placebo group, the ratio of the geometric means showed a statistically significant difference that favoured the group receiving the zinc supplementation: (RR=0.91 [95%CI 0.85 to 0.97]).

Outcome - total stool output

One RCT[180] measured the total stool output. It found that the geometric mean in the intervention group was 111 (95%CI 86 to 147) and 148 (95%CI 116 to 190). The effect size favoured the group receiving the zinc supplementation, Ratio geometric mean 0.69 (95%CI 0.48 to 0.99).

Another RCT [174] compared the total stool output between the groups but the authors reported that the difference found was not statistically significant: geometric mean group receiving 5 mg of zinc 202 (180,246); geometric mean group receiving 20 mg of zinc 229 (180, 256); geometric mean placebo group 240 (200, 266).

Outcome - vomiting

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 4 below. One trial [182] reported that significantly more children given zinc had vomited compared to 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 significant increase of vomiting in children receiving zinc supplementations when compared to children receiving placebo, (significant heterogeneity found (I2 >50%), therefore the random effects model was used RR=1.63 [95%CI 1.11 to 2.40]).

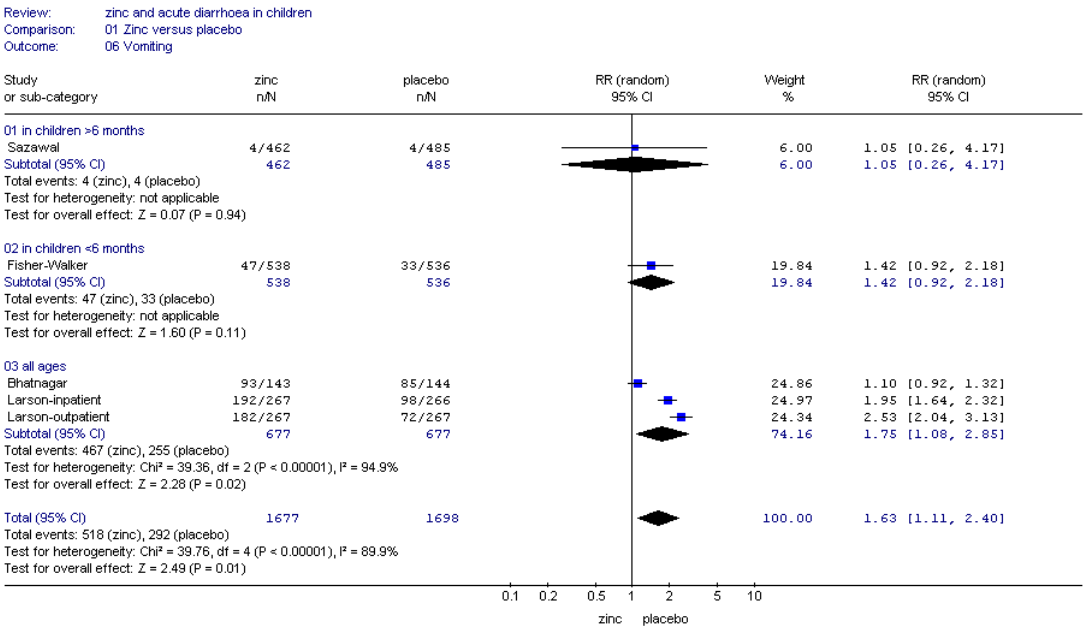


Figure 7

In one trial [184], vomiting was reported as the percentage of days during diarrhoea with vomiting after the enrolment day. It was found that the percentage of days with vomiting was 16% in the intervention group and 8.7% in the placebo group, (RR=1.7 [95%CI 1.4 to 2.2]). The difference found between the two groups was statistically significant and favoured the placebo group.

One study [183] reported that no vomiting occurred during the follow-up among both groups. Another [184]study reported that vomiting events were equal among the children receiving the zinc supplementation and among the children receiving placebo.

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 significant reduction in duration of diarrhoea in zinc supplemented children when compared to the control group, results from a meta-analysis (5 RCTs) did not find a significant reduction. One study reported that significantly more children who had received zinc did not have diarrhoea at day 3 compared to placebo. Meta-analysis performed regarding the proportion of children with diarrhoea by day 7 (4 RCTs) and stool frequency (4 RCTs), showed no statistically significant differences between the zinc and placebo groups, although two studies presenting results for each of these outcomes did report significant improvement with zinc administration. When data from 4 trials were combined it showed a significantly increased number of vomiting events among children supplemented with zinc when compared to children in the control group.

8.3.2 Vitamin A

Evidence overview

Three trials were identified in this review: [185],[186],[187]. Two of these were conducted in Bangladesh ([185],[186]) and one in Turkey [187]. All three had two treatment arms. Across the three studies, data from 286 children (aged 6 months to 7 years) suffering from acute diarrhoea was collected.

Two of the studies were RCTs [185],[186] and reported the method of sequence generation for the assignment of the participants into the two groups. The third study [187] was a quasi-randomised trial where the method of randomisation was based on the patients file numbers (odd or even). Allocation concealment was stated only in two trials ([186],[187]). The outcome assessor was blinded in the three studies. The proportion of patients randomised but lost to follow-up was reported in all the studies

(<20%). Two trials included a sample size power calculation.[186],[187] Comparability of the groups at study entry was adequate in all the 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.

Vitamin A (200 000 IU) versus placebo

Two studies made this compared the effects of vitamin A with placebo in children with diarrhoea [185],[186]

One RCT [185] *n* = 83, examined the therapeutic effect of vitamin A in children suffering from acute diarrhoea. [EL = 1+] The study compared the administration of a single oral dose of 200.000 IU vitamin A with 25 IU vitamin E against the administration of placebo, which consisted on 25 IU vitamin E. The participants were boys aged between 1 and 5 years presenting with watery non-cholera diarrhoea of less than 48 hours duration. The outcomes measured in this RCT were: duration of diarrhoea, stool output, emetic episodes and treatment failure.

One RCT [186] *n* = 90, examined the effects of a single administration 200.000 IU of vitamin A in children with shigella infection against the administration of a placebo. [EL = 1+] The patients were children aged between 1 and 7 years that had presented to the outpatient department with diarrhoeal stools. The outcomes measured in the trial were achievement of clinical and bacteriological cure on study day 5.

Outcome - duration of diarrhoea

The mean total duration of the diarrhoeal episodes in the vitamin A group (*n* = 46) was 52.10 hours (SD 29.40) compared to 54.60 hours (SD 41.70) in the placebo group (*n* = 37).

Only one child in the placebo group and none in the vitamin A group experienced a diarrhoeal episode lasting more than 10 days.

The difference between the two groups were not statistically significant for the total duration of the diarrhoeal episode as well as for the proportion of children with a diarrhoeal episode lasting more than 10 days, WMD=-2.50[95%CI -18.40 to 13.40] and RR=0.27 [95%CI 0.01 to 6.43], respectively. ([185])

Outcome - stool output (g/kg/hour) and total stool output (g/kg) after the start of the treatment

The mean stool output rate was 143 g/kg/hour (SD 133.20) in the vitamin A group (*n* = 46) and 243.60 g/kg/hour (SD 160.70) in the placebo group (*n* = 37). The mean total stool output after the start of the treatment in the vitamin A group was 5.80 g/kg (SD 4.20) compared to 5.50 g/kg (SD 3.90) in the placebo group. The study found no statistically significant differences between the two treatment groups when considering the stool output in the first 24 hours after the start of the intervention or the total stool output, WMD=-0.60[95%CI -65.12 to 63.92] and WMD=0.30 [95%CI -1.45 to 2.05], respectively. ([185])

Outcome - vomiting

The study found no statistically significant difference in the volume vomited per day between the group receiving the vitamin A dose (mean 24.90 g/kg/d, SD 59.80) and the group receiving the placebo (mean 16.50 g/kg/d, SD 46.10), (WMD=8.40 [95%CI -14.39 to 31.19]). ([185])

Outcome - treatment failure

Treatment failure was defined by the researchers as the need for intravenous fluid therapy after initial oral rehydration. The study did not find a statistically significant difference in the rate of treatment failure between the children treated with vitamin A (5/46) and the children receiving the placebo (4/37), (RR=1.01 [95%CI 0.29 to 3.48]).

Outcome – 'clinical cure'

This outcome 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]). ([186])

Outcome – 'bacteriological cure'

Bacteriological cure was defined as the continuous absence of shigella in both, stool and rectal swab samples, from study day 3 onwards. Sixteen children in each group were bacteriologically cured by day 3. No statistically significant difference in bacteriological cure was found between the two groups, (RR=0.98 [95%CI 0.57 to 1.68]). ([186])

Vitamin A (100 000 IU) versus placebo

A quasi-randomised controlled trial [187] 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. [EL = 1−] The 120 children enrolled in the study were infants aged between 6 and 12 months suffering from acute diarrhoea for less than five days, those with malnutrition, dysentery or a chronic condition were excluded. The outcomes measured were duration of diarrhoea and persistent diarrhoea.

Outcome - total duration of diarrhoea after the start of the study

Cessation of diarrhoea was defined as passage of formed stool as described by the mother for at least 24 hours. The mean total duration of diarrhoea was 3.80 days (SD 2.30) in the vitamin A group (n = 60) and 3.90 days (SD 1.90) in the placebo group (n = 60). This difference was not statistically significant (WMD=-0.10 [95%CI -0.85 to 0.65]).

Outcome - persistent diarrhoea

Two patients in each group had persistent diarrhoea. The finding was not statistically significant (RR=1.00 [95%CI 0.15 to 6.87]).

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 and number of treatment failures when comparing children that received 200.000 IU of vitamin A against 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 the day five than the placebo children. The trial did not show a significant difference between the two groups when considering bacteriological cure. The quasi-RCT showed no difference in duration of diarrhoea and 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 (Songul Yalcin 2004).

The study was a quasi-randomised controlled trial in which a total of 159 infants were enrolled. Eligible cases in the study were divided in two groups according to their hospital file number on admission, hence allocation concealment was inadequate. The authors reported that patients 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. Lost to follow-up was nearly 20%. The comparability between the two groups at the start of the trial was adequate.

Glutamine versus no placebo

The trial assessed the effect of administering 0.3 g/kg/day of glutamine in the treatment of acute diarrhoea in children. [EL = 1−] Mothers administered the supplement (glutamine or placebo) in three

daily doses for 7 days. Participants were children aged from 6 to 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. The outcome considered was duration of the diarrhoeal episode.

Outcome - duration of diarrhoea

The mean duration of diarrhoea in the group receiving glutamine (*n* = 63 mean 3.40 days, SD 1.96) was shorter than in the control group (*n* = 65 mean 4.57 days, SD 2.48). This finding was statistically significant (WMD=-1.17 [95%CI -1.94 to -0.40]).

Outcome - duration of diarrhoea after treatment

Data were stratified by stool frequency on admission. Children in the glutamine group with a stool frequency< 8/day (*n* = 46) had a mean duration of diarrhoea of 3.30 days (SD 1.96) compared to 4.68 days (SD 2.60) in those receiving the placebo (*n* = 41). This finding was statistically significant (WMD=-1.38 [95%CI -2.36 to -0.40]). When the data collected from the children with high stool frequency, >8 stools/day, were analyzed, no statistically significant difference in mean duration of diarrhoea (WMD=1.28 [95%CI -0.03 to 2.59]) was observed between the glutamine group (*n* = 17, mean 3.65 days, SD 1.97) and the placebo group (*n* = 24, mean 2.37 days, SD 2.30).

Outcome - proportion with persistent diarrhoea

3.2% of the glutamine group (2/63) and 9.2% in the placebo group (6/65) had persistent diarrhoea but the difference between the groups was not statistically significant (RR=0.34 [95%CI 0.07 to 1.64]).

Outcome - vomiting

Vomiting was observed in 24 out of 63 infants in the intervention group and in 32 out of 65 in the placebo group. The finding was not statistically significant (RR=0.77 [95%CI 0.52 to 1.15]).

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 RCT conducted in Turkey [EL = 1−] showed no difference in the onset of persistent diarrhoea and vomiting. On the other hand, the study suggested that glutamine supplementation shortens the duration of diarrhoea by one day.

8.3.4 Folic Acid

Evidence overview

A single study located in Bangladesh was identified as relevant and included in the review ([178]). This RCT recruited 106 male children suffering from acute watery diarrhoea. The participants were randomised in two treatment arms, the intervention group (*n* = 54) and the control group (*n* = 52). Method of randomisation and allocation concealment were not reported by the authors. Subjects and investigators were blinded to the treatment administered and the baseline comparability between the two groups was adequate. Lost to follow-up was not reported. Power calculation was performed.

Folic Acid versus placebo

The study evaluated the clinical benefit of oral folate in the treatment of acute diarrhoea in young children. [EL = 1+] The trial compared the effect of administering folic acid in a dose of 5 mg at 8 hours intervals for 5 days against the administration of placebo. Male children, aged between 6 to 23 months, who presented with watery diarrhoea (of less than 72 hours duration) and some degree of dehydration were enrolled after admission into the study ward. The outcomes measured were course of illness, stool output, ORS intake and IV fluids received.

Outcome - duration of diarrhoea

The mean duration of diarrhoea in the group receiving folic acid was 108 hours (SD 68.00) and 103 hours (SD 53.00) in the group receiving placebo. This difference was not statistically significant (WMD=-18.16 [95%CI -18.16 to 28.16]).

44% children receiving the folic acid (24/54) and 42% children receiving placebo (22/52) had diarrhoea beyond 5 days. The difference between the two study groups was not statistically significant (RR=1.05 [95%CI 0.68 to 1.62]) .

Outcome - total stool output

The mean total stool output in the group receiving folic acid was 532 g/kg (SD 476.00) and 479 g/kg (SD 354.00) in the placebo group. The difference between the groups was not statistically significant (WMD= 53.0[95%CI -106.3 to 212.3]).

Outcome - total ORS intake

The mean total intake of oral rehydration solution in the folic acid group was 511 g/kg (SD 457.00) and 546 g/kg (SD 355.00) in the placebo group. This was not a statistically significant finding (WMD= -35.00[95%CI -190.46 to 120.46]).

Outcome - proportion of children receiving iv fluid therapy

The researchers found that 4% children in the intervention group (2/54) and 10% children in the control group (5/52) required intravenous fluid therapy. There was no statistical significance in the result (RR= 0.39[95%CI 0.08 to 1.90]). Data were also analysed for rotavirus-positive children (n = 63) and the results did not show any significant difference 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 five day folate supplementation for the treatment of children with acute diarrhoea did not reduce the duration of diarrhoea, the stool output, the ORS intake and the number of children requiring intravenous fluid therapy.

8.3.5 Fibre

Evidence overview

Two RCTs were included.[188;189] One of the studies was conducted in Peru [188] and the other in the US [189]. Both trials had two treatment arms. In total they recruited 91 children with acute diarrhoea. One study was community-based [189] (n = 57) and the other was hospital-based [188](n = 34). Both studies were double-blinded, placebo controlled RCTs and both reported an adequate randomisation method. Allocation concealment was however unclear in the two studies. The sample size power calculation was not reported in neither of the two studies. The proportion of participants lost to follow-up was 15% in the Brown study and 25% in the US study. Comparability of the groups at study entry was adequate in all the two studies.

Soy protein formula with versus without added fibre (0.6 g/ml)

One RCT [188] n = 34, examined the therapeutic effect of dietary fibre on the severity and duration of acute watery diarrhoea. [EL = 1−] The study compared the effects of the administration of a soy protein lactose free formula with added fibre against the administration of a soy protein formula without formula in children. The participants were hospitalised male children aged between 2 and 24 months suffering from acute diarrhoea for less than 96 hours. 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 >5%, electrolyte disorders after initial rehydration or important faecal output during intervention).

One community-based RCT[189], *n* = 55, assessed the efficacy of dietary fibre in reducing the duration of watery diarrhoea in middle-class American children. [EL = 1−] The trial compared the effects of feeding children aged less than 24 months with a soy-fibre supplemented infant formula for ten days against a standard soy formula in shortening the duration of acute diarrhoea. The main outcome measured was mean duration of diarrhoea in hours.

Outcome - duration of diarrhoea

Two trials presented data on the duration of diarrhoea. One trial [188] defined duration of diarrhoea 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. 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, $p<0.003$.

One trial [189] presented additional results 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 in the control group, $p<0.05$.When they compared the mean duration of diarrhoea in infants aged < 6 months (17.5 hours in the group receiving fibre and 8.1 hours in the control group), the difference was statistically insignificant. The authors reported for all children that there was a statistically insignificant 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).

Outcome - treatment failure

One study [188] reported that 21% of children receiving the soy protein formula with added fibre (4/19) and 13% of children receiving the soy protein formula without added fibre (2/15) were reported as treatment failures. The difference between the two groups was not statistically significant, (RR=1.58 [95%CI 0.33 to 7.49]).

Evidence summary

There was a lack of high quality evidence [EL = 1−] on the clinical effectiveness of administering soy protein formula with added fibre (0.6 g/ml) in children with acute diarrhoea. Data from one RCT located in Peru showed a 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 US suggested that in children aged >6 months, supplementation with fibre shortened the duration of diarrhoea by more than 12 hours.

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 of that zinc treatment was 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 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, 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. However, the trails were not of high quality

8.4 Probiotics

In 1985 a lactobacillus was identified through screening of bacteria in fermented milk products which was acid and bile resistant, adhered to intestinal epithelial cells.[190],[140] This was *Lactobacillus GG*, a non-pathogenic organism. The current view of probiotic therapy is based on the concept of a normal balanced intestinal microbiota [191] 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 bacteriocidans, promotion of mucin production., upregulation of genes mediating immunity, and production of trophic short chain fatty acids to promote mucosal cell growth and differentiation.[191] 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 [192],[193],[194] and 4 RCTs.[195],[196],[41],[197]

One systematic review [192], published in 2003, was conducted to examine the effectiveness of probiotics in the treatment of infectious diarrhoea. [EL = 1++] This well-conducted systematic review included 23 RCTs published between 1981 and 2002. Fourteen studies were carried out in developing countries. The selected studies enrolled a total of 1917 participants. Of these, 1449 were children (740 were randomised in the intervention group and 709 in the control group) and 352 were adults (173 were randomised in the intervention group and 179 in the control group). 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 participants 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 was not uniform and only three studies reported adequate method of randomisation, allocation concealment, blinding and loss to follow-up. Different types of probiotics 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 was 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 intravenous fluid therapy and death.

8.4.1 Lactobacillus and saccharomyces yeast probiotics

Probiotic versus control

Outcome - diarrhoea lasting 3 or more days

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 (I2=46.6%) between studies. When data from children were pooled (11 RCTs, *n* = 1008), the analysis also showed that significantly more of those receiving placebo (265/490) had persistence of diarrhoea on day 3 compared to those receiving probiotics (195/518) : (RR=0.68 [95%CI 0.54 to 0.85]), I2=50.2%.

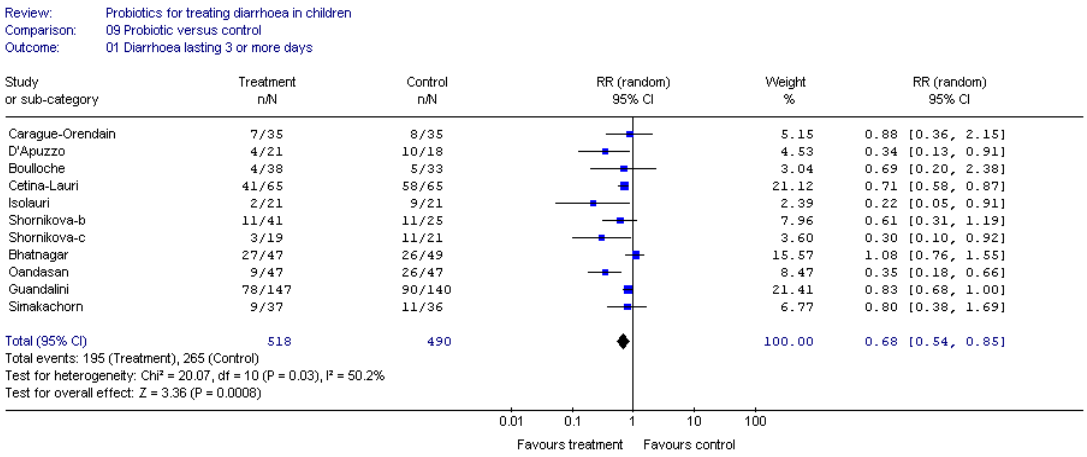


Figure 8

Outcome - diarrhoea lasting 4 or more days

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 probiotic when compared to the control group was (RR=0.31 [95%CI 0.19 to 0.50]). However, there was heterogeneity between studies (I2=72.9%).

A meta-analysis pooling together the data from 9 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 to those receiving probiotics (79/459) : (RR=0.26 [95%CI 0.13 to 0.52]), I2=62%.

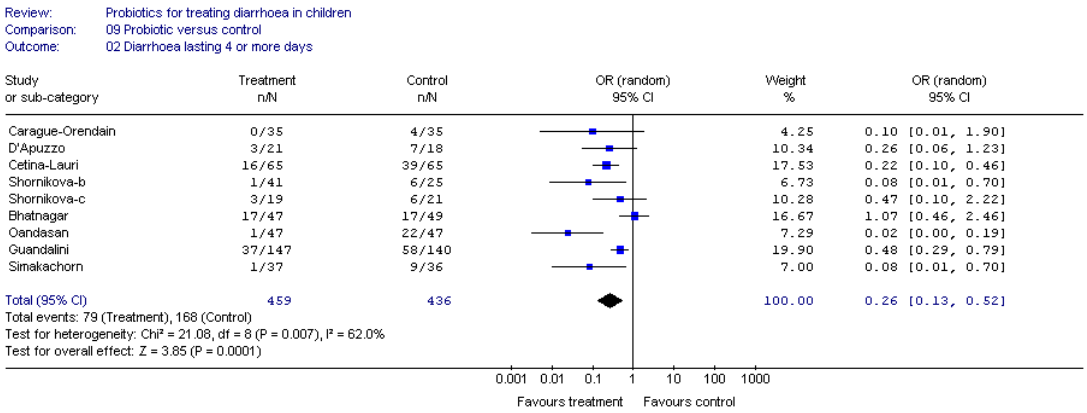


Figure 9

Outcome - duration of diarrhoea

The mean duration of diarrhoea was measured in 12 studies that included only children. Those children receiving the probiotic agent had a significantly shorter duration of diarrhoea when compared to the children in the control group, (WMD=-30.48 [95%CI -42.46 to -18.51]), random effect model (I2=85.6%).

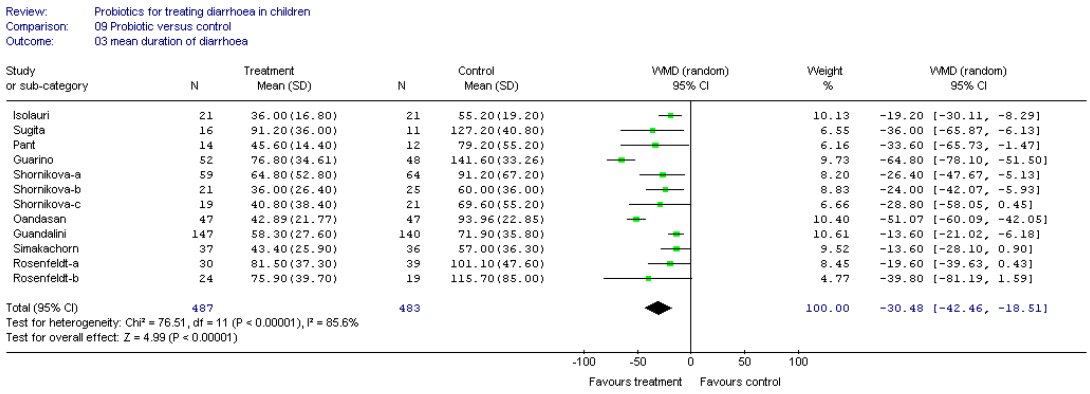


Figure 10

Outcome - stool frequency on day 2 and on day 3 of the intervention

Mean stool frequency on day 2 was reported in 5 trials (*n* = 417) and on day 3 it was reported in 4 trials (*n* = 447). Participants in the probiotic group had fewer stools:

- on day 2 of intervention (WMD=-1.51 [95%CI -1.85 to -1.17])
- 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 was included in a meta-analysis:

- on day 2 (4 RCTS, *n* = 232): the analysis showed that children treated with probiotics passed significantly fewer stools than those receiving placebo, (WMD=-1.01 [95%CI -1.66 to -0.36]).
- on day 3 of intervention (2 RCTs, *n* = 170): the analysis showed that children in the probiotic group passed significantly fewer stools than children in the control group, (WMD=-1.12 [95%CI -1.79 to -0.46]).

Outcome - intravenous rehydration therapy

The review reported that occasionally children developed severe dehydration requiring parenteral fluid therapy but in none of the studies this was attributable to the administration of the probiotic agent.

Death

No death events were recorded among the included studies.

Evidence summary

There was evidence from a well-conducted systematic review [EL = 1++] examining the effectiveness of probiotics compared to 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.

8.4.2 *Lactobacillus rhamnosus* GG

One systematic review[193] evaluated the effectiveness of *Lactobacillus rhamnosus* GG in the treatment of acute infectious diarrhoea in children. [EL = 1+]

This well-conducted systematic review included 8 RCTs involving 988 participants, 494 in the intervention group and 494 in the control group. From the 8 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, inpatients as well as outpatients. They presented with different grades of dehydration and duration of diarrhoea prior to enrolment (even if in most of the trials participants were mildly dehydrated and had diarrhoea for less than 3 days prior 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 8 RCTS was heterogeneous: method of randomisation and allocation concealment were unclear or inadequate in 4 and 6 studies respectively, 2 trials were not blinded and 3 trials did not include an ITT analysis. In one study 43% of the participants enrolled did not complete the follow-up. Data was 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.

Lactobacillus rhamnosus GG versus control

Outcome - duration of diarrhoea (days)
Seven trials measured the duration of diarrhoea (*n* = 876). The authors of the review performed a meta-analysis (high heterogeneity I2=97.4%) showing that children receiving the *L* GG, compared to children in the control group, experienced a reduction of one day in the duration of the diarrhoeic episode, (WMD=-1.08 [95%CI -1.87 to -0.28]).

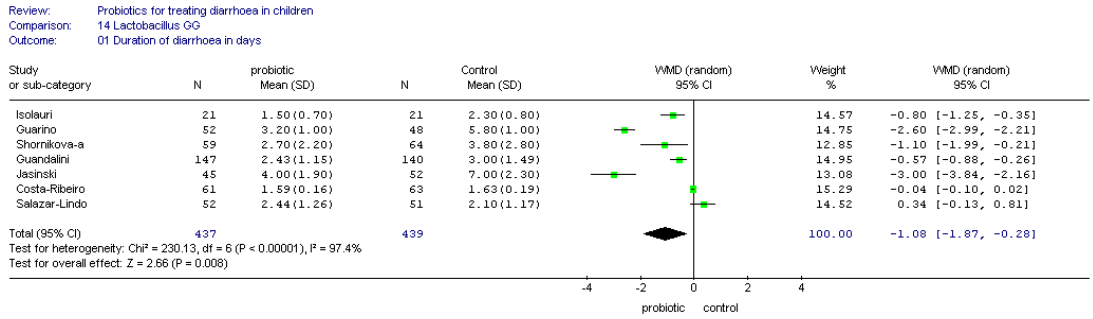


Figure 11

Three trials reported the duration of rotavirus diarrhoea in children (*n* = 201). The data were pooled, despite high heterogeneity (I2=94%), showing that children in the intervention group had a two-days shorter diarrhoea than those children in the control group, (WMD=-2.08 [95%CI -3.55 to -0.60]).

Outcome - total stool output (ml/kg)
Two RCTs (*n* = 303) showed no significant difference between the children treated with the probiotic and the children in the control group, (WMD=8.97[95%CI -86.26 to 104.20]).

Outcome - hospitalisation
Three studies were combined (I2=86.4%) showing that hospitalisation was shorter among children receiving the *L*GG than among children in the control group, (WMD=-0.43[95%CI -1.32 to 0.46]). However, the difference was not statistically significant.

Outcome - vomiting
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 on the frequency of vomiting in day 1, (WMD=-0.2[95%CI -2 to 1.7]). On day 2 the difference was significant favouring the intervention group, (WMD=-2.95[95%CI -3.4 to -0.6]).

1) Adverse events

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 7 trials was combined showing that children treated with *Lactobacillus rhamnosus* GG experienced one day reduction in the duration of diarrhoea but there was significant statistical heterogeneity. Analysis performed on total stool output and hospitalisation showed no significant difference between children receiving *Lactobacillus rhamnosus* GG and children that did not receive the probiotic.

8.4.3 *Lactobacillus acidophilus* LB

Evidence overview

One RCT was identified[197]. This study, conducted in Peru, randomised a total of 80 children with diarrhoea presumed to be of infectious origin into two treatment arms (40 participants in each group). Method of randomisation and allocation concealment were unclear. However, the study was double-blinded and the baseline comparability of the two groups at the start of the study was adequate. Three participants out 80 were lost to follow-up. The outcomes considered were duration of diarrhoea, proportion of children with diarrhoea at the end of the study, total ORS intake and adverse events. .

Lactobacillus acidophilus LB versus placebo

The study was aimed to determine the effect of *Lactobacillus* LB in the treatment of acute diarrhoea in children. [EL = 1+] It compared the administration *Lactobacillus acidophilus* LB for four days and a half against placebo in children with acute diarrhoea. Children with signs of dehydration requiring hospitalisation and those with illnesses other than the acute diarrhoeal episode were excluded.

Outcome - Duration of the diarrhoea in hours (median and inter-quartiles)
The authors found that the group receiving the probiotic had a shorter duration of diarrhoea after randomisation (median 10 hours, quartile1: 6/quartile3: 56.7) than the control group (median 16.6 hours, quartile1: 7.1/ quartile3: 50.3), this finding was reported in the study as not statistically significant.

Outcome - proportion of children without diarrhoea at the end of the intervention (108 hours)
36 children out of 40 in the probiotic group and 35 children out of 40 in the placebo group had their diarrhoea resolved by the end of the study. The difference between the two groups was not significant (RR=1.03 [95%CI 0.88 to 1.20]).

Outcome - total ORS intake
The authors reported that the total intake of ORS was similar in both groups. No other details were provided.

Outcome - vomiting
12 of 40 children in the probiotic group and 6 children out of 40 in the placebo group vomited. The difference between the two groups was not significant (RR=2 [95%CI 0.83 to 4.81]).

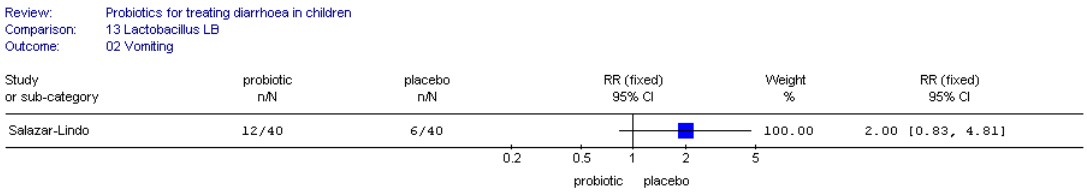


Figure 12

Adverse events
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 significant differences between the probiotic group and the placebo group when considering duration of diarrhoea, ORS total intake, vomiting, adverse events and proportion of children without diarrhoea by the end of the study.

8.4.4 *Lactobacilllus paracasei* strain ST11

Evidence overview

One RCT [196] was identified. This trial was located in Bangladesh. In total, 230 male infants and young children with acute diarrhoea were randomly divided in two treatment arms. Participants were followed in hospital for 6 days or until cessation of diarrhoea. The method of randomisation, allocation concealment and baseline comparability of the two groups under study were adequate. The trial was double-blinded and the lost to follow-up was less than 20% (11.8%). The outcomes measured were mean duration of diarrhoea, cessation of diarrhoea, total stool output and total ORS intake.

Lactobacillus paracasei ST11 versus placebo

The study (n = 230) evaluated the therapeutic benefit of administering lyophilised *L. paracasei* strain ST11 for five days in the course of acute diarrhoea. [EL = 1+] It compared the administration of the probiotic with placebo in children aged from 4 to 24 months suffering from diarrhoea for less than 48 hours. Children with bloody-diarrhoea, with severe malnutrition or requiring antibiotic-therapy were excluded. Children whose stool sample resulted positive to *Vibrio cholerae* were also excluded.

Outcome - duration of diarrhoea (hours)
The mean duration of diarrhoea in the probiotic group was 90.40 hours (SD 45.00) and 94.20 hours (SD 43.30) in the placebo group. This result was not statistically significant (WMD=-3.8 [95%CI -15.21 to 7.61]).

Outcome - cessation of diarrhoea
The number of children without diarrhoea by the end of the 6th day of the study was higher in the intervention group (81/115) when compared to the placebo group (73/115) but the difference was not statistically significant, (RR=1.11 [95%CI 0.92 to 1.33]).

Outcome - total stool output (g/kg) and total ORS intake (ml/kg)
The study reported the mean total stool output and the mean total ORS intake. The mean total stool output was 385.00 g/kg (SD 330.00) in the probiotic group and 389.00 g/kg (SD 259.00) in the group receiving placebo. The mean total ORS intake was 334 ml/kg (SD 280.00) in the probiotic group and 343.00 ml/kg (SD 230.00) in the group receiving placebo. Neither of the results were statistically

significant (WMD=-4 [95%CI -80.67 to 72.67]) and (WMD= -9 [95%CI -75.23 to 57.23] respectively).

Outcome - children requiring intravenous fluids

Only one child in the intervention group (n = 115) and four in the control group (n = 115) required further intravenous fluid therapy. The difference was not significant (RR=0.25 [95%CI 0.03 to 2.20]). The authors measured the above outcomes in rotavirus-infected (n = 130) but they found no statistically significant differences between the two groups under study. When non rotavirus-infected children were considered (n = 63) the probiotic showed to have a significant positive effect in reducing the total ORS 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* ST11 in the management of acute diarrhoea in children. The study found no 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 intake, the number of children without diarrhoea by the end of the study and 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.

8.4.5 *Lactobacillus rhamnosus* strains 573l/1, 573l/2 and 573l/3

Evidence overview

One RCT was identified.[41] This trial, conducted in Poland randomised a total of 93 children with acute diarrhoea were into two treatment arms. Method of randomisation, allocation concealment and baseline comparability of the two groups were adequate. More than 90% of the enrolled participants were included in the study analysis. Study members and patients were blinded to the group treatment. The outcomes considered were duration of diarrhoea, diarrhoea lasting more than 7 days, intravenous therapy and adverse events.

Lactobacillus rhamnosus strains 573l/1 + 573l/2 + 573l/3 versus placebo

The study assessed the effectiveness of administering *L. rhamnosus* strains 573L/1, 573L/2 and 573L/3 for five days in acute diarrhoea in children. [EL = 1+] Participants were children between 2 months and 6 years of age suffering from diarrhoea. Patients with chronic diseases, immunosuppressive conditions or exclusively breastfed were excluded.

Outcome - duration of diarrhoea

The study found that treated children had diarrhoea for a shorter period of time (n = 46, mean 83.60 hours, SD 55.60) than untreated children (n = 41, mean 96.00 hours, SD 71.50) but that the difference was not significant, (WMD=-12.4 [95%CI -39.55 to 14.75]).

In rotavirus-infected patients (n = 39), children treated with the probiotic had a shorter duration of diarrhoea (n = 22, mean 77.50 hours, SD 35.40) than children that received placebo (n = 17, mean 115.00 hours, SD 66.90). This difference was statistically significant (WMD=-37.50 [95%CI -72.57 to -2.43]).

Outcome - diarrhoea lasting >7 d

Three diarrhoea cases lasting more than 7 days were observed among the children receiving the probiotic (n = 46) while seven cases were found in the placebo group (n = 41). The difference was not significant (RR=0.4 [95%CI 0.11 to 1.45]).

Outcome - intravenous therapy

On admission, children were rehydrated per os or intravenously according to ESPGHAN recommendations. The authors reported the mean duration of parenteral rehydration required was 16 hours (SD 19.30) in the probiotic group and 24.30 hours (SD 29.10) in the placebo group. This

difference between the two groups was not statistically significant (WMD=-8.30 [95%CI -8.30 to 2.21]).

The duration of parenteral rehydration required was significantly shorter among children treated with the probiotic (*n* = 22, mean 14.90 hours, SD 13.70) when compared to children receiving placebo (*n* = 17, mean 37.70 hours, SD 32.90). This difference between the two groups was statistically significant (WMD=-22.8[95%CI -39.45 to -6.15]).

Adverse events
No adverse events were reported.

Evidence summary

An RCT located in Poland showed no significant differences between the children receiving a probiotic preparation of *Lactobacillus* 573L/1, 573L/2 and 573L/3 and the children receiving placebo. When only rotavirus-infected children were considered, the trial showed a significant clinical benefit of the probiotic in reducing the duration of diarrhoea and the duration of the iv fluid therapy required.

8.4.6 *Saccharomyces boulardii*

One systematic review [194] evaluated the therapeutic effects of *Saccharomyces boulardii* in the treatment of acute diarrhoea in children. [EL = 1+]

The review included 5 RCTs involving a total of 619 participants. Of these, two were located in Pakistan, one in Mexico, one in Turkey and one in Argentina. Participants were children between 2 months and 12 years old suffering from diarrhoea. The systematic review was well-conducted. However, all the studies included presented 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 the intention to treat analysis.

Meta-analysis 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 day 2 and 8, presence of diarrhoea at several time intervals, hospitalisation and vomiting.

***Saccharomyces boulardii* versus control**

Outcome - duration of diarrhoea
The meta-analysis performed (4 RCTs, *n* = 473) showed that children receiving the probiotic had a significantly shorter duration of the diarrhoeic episode, (WMD=-1.08 [95%CI -1.3 to -0.83]).

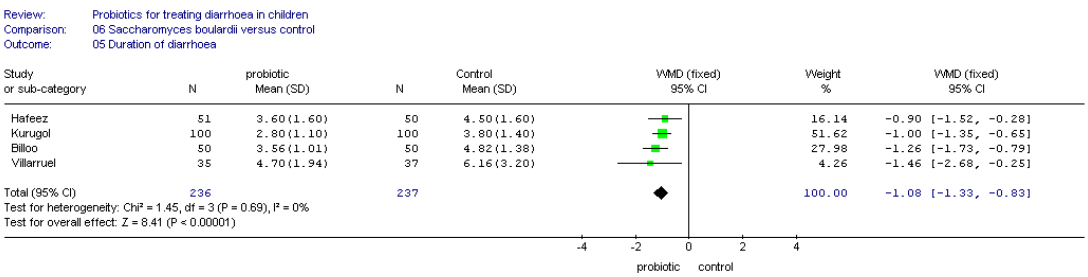


Figure 13

Outcome - number of stools on day 3 and on day 4
Data from 3 RCTs (*n* = 331) was combined in a meta-analysis. It showed that children receiving the probiotic had significantly fewer stools on day 3 when compared to the control group, (WMD=-1.3 [95%CI -1.9 to -0.63]).

The results of two RCTs (*n* = 218) were pooled and showed a significant reduction in the number of stools on day 4 in those children receiving the probiotic, (WMD=-1.1 [95%CI -1.6 to -0.64]).

Outcome – 'cure' on day 2 and on day 8

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 significantly more children in the intervention group experienced cessation of diarrhoea on both study days, when compared to the control group, (RR=4 [95%CI 1.8 to 9.1]) and (RR=1.9 [95%CI 1.4 to 2.8] respectively).

Outcome - presence of diarrhoea at different time intervals

The proportion of children with diarrhoea on day 3 and 6 was reported in one study (*n* = 101). The study found that the children in the intervention group were more likely to be diarrhoea-free by day 3 and 6 when compared to the children in the control group: (RR=0.71 [95%CI 0.56 to 0.9]) and (RR=0.49 [95%CI 0.24 to 0.99]).

Another study (*n* = 88) measured the presence of diarrhoea on day 4. It found no significant difference between the two groups, (RR=0.73[95%CI 0.5 to 1.1]). The same study (*n* = 88) measured the proportion of children with diarrhoea on day 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 significantly more likely to be diarrhoea-free on day 6 and 7 when compared to the control group, (RR=0.49 [95%CI 0.24 to 0.99]) and (RR=0.39 [95%CI 0.20 to 0.75]). In addition, the number of children with diarrhoea lasting more than a week was significantly higher in the control group, (RR=0.25 [95%CI 0.08 to 0.83]).

Outcome - hospitalisation (days)

One RCT (*n* = 200) found that children who were treated with *S. boulardii* had a significantly shorter stay in hospital than those children who did not receive the probiotic (RR=-1 [95%CI -1.4 to -0.62]).

Outcome - vomiting

One RCT (*n* = 200) included in the review measured the duration of vomiting in days. It found no statistically significant differences between the two groups, (WMD=-0.1 [95%CI -0.34 to 0.14]).

Adverse events

Adverse events associated with the administration of S. 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 one day and resulted in fewer stools on days 3 and 4, but the authors reported methodological limitations in the included trials.

8.4.7 *Escherichia coli* Nissle 1917

Evidence overview

One multi-centred RCT [195] was identified. The study was carried out in Ukraine, Germany and Russia. In total 113 children with non-bloody acute diarrhoea were randomised in two treatment arms (58 patients in the intervention group and 55 in the placebo group). The participants were allocated in the two groups based on random numbers. Allocation concealment, double-blinding and baseline comparability between the two groups at the start of the study were adequate. 12.3% participants were lost to the follow-up. 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.

E. coli versus placebo

The study (*n* = 113) examined the therapeutic value of the probiotic *E. coli* Nissle in children treated for acute non-bloody diarrhoea in 11 paediatric outpatient centres across Ukraine, Germany and Russia. [EL = 1+] It compared the administration of *E. coli* Nissle against placebo until treatment response (10 days at maximum). The children included in the study were aged between 2 and 47 months.

Outcome - time to response

The treatment response was defined as a reduction in stool frequency to < = 3 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 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.

Outcome - patients without diarrhoea within the 10th day of the intervention

The authors reported that in 52 out of 55 children in the intervention group and in 39 out of 58 children in the control group, diarrhoea stopped within 10 days. The difference was statistically significant, (RR=1.41 [95%CI 1.16 to 1.70]).

Adverse events

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 form one multicentre RCT conducted in Russia, Ukraine and Germany [EL = 1+] for the effectiveness of *E. coli* Nissle in the treatment of acute diarrhoea in children. The study reported that those children receiving *E. coli* Nissle probiotic responded to treatment in a significantly shorter time than those receiving placebo. Diarrhoea had stopped by day 10 in significantly more children receiving *E. coli* Nissle probiotic compared to 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 regimes used, and in the outcomes examined. Licensed preparations of probiotics are not currently available in the NHS, Thus, despite some evidence of possible clinical benefit, the GDG did not consider it appropriate to recommend the use of probiotics at this time. It was considered an important field for further research.

Research recommendation

Further randomized controlled trials should be undertaken to further evaluate the effectiveness and safety of specific probiotic agents.

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.[198]

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. [198]

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 and 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.[198]

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.[198]

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

Despite searches being performed 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 guideline 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 (refer to 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 to 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' 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 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 concept [199] 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) 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 of those with symptoms suggestive of shock to a secondary care facility
- refer for face-to-face assessment those with:
  - symptoms suggesting an alternative serious condition
  - factors indicating an increased risk of dehydration
  - symptoms suggesting clinical dehydration
  - adverse social or family circumstances
- provide appropriate safety netting arrangement to ensure continuity of care and early recognition of clinical deterioration.

During community face-to-face assessment:

- immediately refer (by emergency transfer) to a secondary care facility all children with symptoms and signs of shock
- using clinical judgement, consider early repeat face-to-face reassessment or referral to a secondary care facility those with:
  - symptoms and signs suggesting an alternative and serious diagnosis
  - dehydration associated with red flag symptoms or signs
  - adverse social or family circumstances
- provide appropriate safety netting arrangement to ensure continuity of care and early recognition of clinical deterioration.

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.

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

Advise parents and carers:

- in children without clinical dehydration and who 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
- in children without clinical dehydration 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
  - offer ORS as additional supplemental fluid
- in children with clinical dehydration:
  - that rehydration is usually possible with oral rehydration solution (oral rehydration therapy)
  - to make up the ORS according to the instructions on the packaging
  - to give the specified amount of ORS (50 ml/kg for rehydration plus maintenance volume) over a 4 hour period
  - to give this amount of ORS in small but frequent feeds
  - to continue breast feeding in addition to giving the ORS
  - to be concerned if
    - the child refuses to take the ORS or persistently vomits

    - o does not appear to be recovering
    - o appears to have become less well
  - to seek advice from a specified healthcare professional if they are concerned
- following rehydration:
  - child should be encouraged to drink plenty of their usual fluids including milk feeds if these were stopped
  - to reintroduce the child's usual diet
  - to give a specified volume of ORS (5 to 10 ml/kg) following the passage of large watery stools in children at increased risk of dehydration
- that the usual duration of diarrhoea is 5 to 7 days and in most children it resolves within 2 weeks
- that the usual duration of vomiting is 1 or 2 days and in most children it resolves within 3 days
- to seek advice from a specified healthcare professional if children's symptoms are not resolving as expected.

Prevention of 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 [35,36] 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 prevention of primary spread of diarrhoea and vomiting

Advise parents and child carers that: *

- handwashing with soap (liquid where possible) in warm running water and careful drying is the most important factor in the prevention of spread of diarrhoea and vomiting.
- handwashing should occur after going to the toilet (children) or changing nappies (parents) and before the preparation, serving or eating of food.
- towels used by infected children should not be shared.
- children should not attend any childcare facility or school when diarrhoea or vomiting is present.
- following any episode of diarrhoea and vomiting, children under 5 years old can return to school or other child care facility 48 hours following the last episode of diarrhoea or vomiting.
- children should not swim in swimming pools for 2 weeks following the last episode of diarrhoea.

* These recommendations are taken from guidelines commissioned by the Department of Health.[35;36]

Appendix A

Cost effectiveness of IVT v ORT for children with dehydration

Introduction

Acute diarrhoea with or without vomiting accounts for approximately 20% of GP consultations and more than 12% of emergency department presentations each year, clearly a substantial proportion of NHS resources. Currently, there are wide variations in current practice in both primary and secondary care in methods of rehydration therapy used in treating children presenting with dehydration. The GDG identified a single clinical question comparing the effectiveness and safety of oral rehydration therapy (ORT) against intra-venous 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 which were clearly not relevant to the research question being addressed and from this 6 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 ORT.

From the 6 retrieved papers, only one paper[200] was identified as an economic evaluation.

This study aimed to compare nasogastric and intravenous methods of rehydration for children with acute dehydration in a US setting for children aged between 3 to 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 means of resolving their dehydration were enrolled onto 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 which included laboratory, supply and staff costs. The cost analysis aimed to measure any saving as a result of using RNG over RIV. Authors do not report any significant complications for RNG; RIV is reported to be complicated by repeated catheter insertions which the authors felt resulted in greater inconvenience, pain and an increase overall cost of care.

No statistical difference in outcomes was found between the two treatment options and the authors therefore conclude that RNG is more cost-effective than RIV, on cost alone. Furthermore, the authors note that both RIV and RNG are cost-effective alternatives to standard treatment (IVT). The authors also conclude that RNG has fewer associated complications in comparison to 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 intravenous therapy, whereas the clinical question for this guideline sought to compare the cost-effectiveness of ORT, more broadly

defined, versus standard IVT. Due to the lack of relevant published economic evidence, it was decided that a decision-analytic model should be developed for the 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 Figures 1-3 below. The economic model focuses on a cohort of 1,000 hypothetical patients presenting in A&E with mild/moderate dehydration caused by D&V.

The decision tree depicts the various pathways it is assumed a child may follow during treatment of either IV 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 3 types:

- Decision nodes (blue squares) are used to represent choices for the decision maker, in this case the choice to give IVT or ORT.
- Chance nodes (green 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 (red 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.

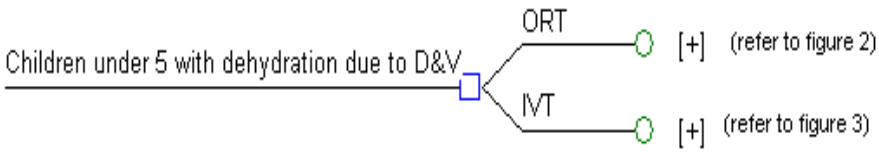


Figure 1 Truncated Version of the Decision Tree: the full sub-tree [+] for both IVT and ORT is shown separately

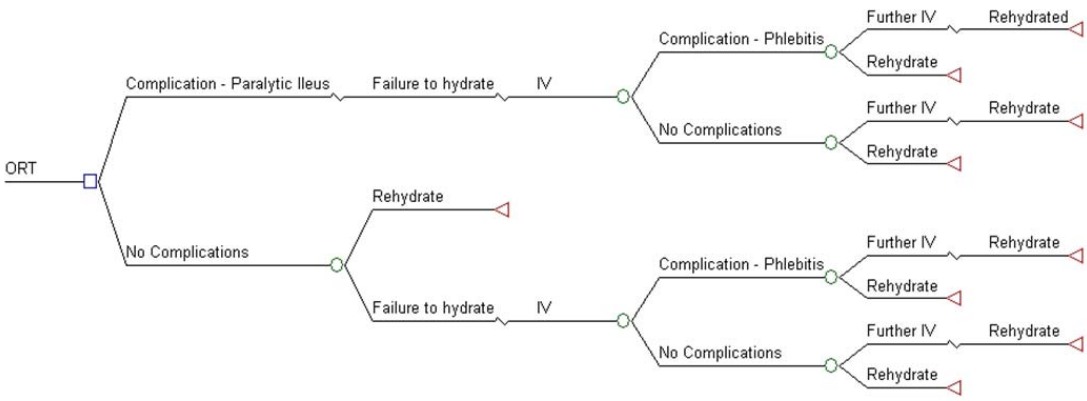


Figure 2 ORT sub-tree

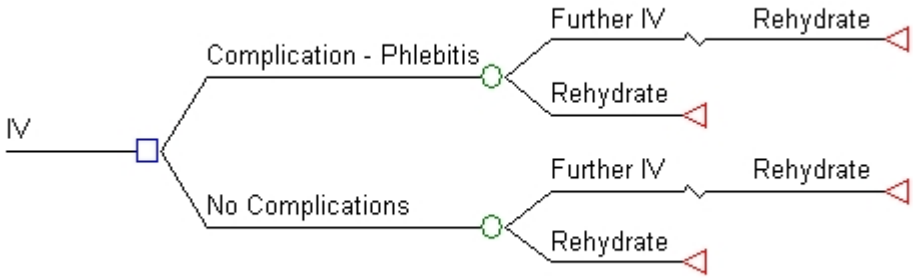


Figure 3 IV sub-tree

Model parameters and assumptions

Probabilities

Model probabilities are taken from a Cochrane review [201]. This review reported on the evidence on rehydration and complication rates for ORT and IVT in children up to 18 years of age and their findings are summarised in Table 1.

Table 1 Meta analysis of rehydration and complication rates for ORT and IVT

	ORT	IVT
Outcome	*Rate*	*Rate*
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[a]	0.000	0.027
Peri-orbital oedema	0.026	0.026

	ORT	IVT
Abdominal distension	0.017	0.000
Seizures	0.000	0.000

[a] Indicates statistical significance at the 5% level

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 model we have assumed that ORT treatment "failure" is that where IVT would have to be used. Theoretically IVT should be able to replace fluid lost and manage ongoing 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 "further IV". It is assumed 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 which was statistically significant at the 5% level. As a result the only complications modelled were phlebitis and paralytic ileus. Table 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.

Table 2 Probabilities used in the analysis

Item	Value	Range	Source	Notes
Failure to rehydrate on ORT with paralytic ileus	1.00	N/A	GDG	
Failure to rehydrate on ORT with no paralytic ileus	0.039	0.039-0.042	Hartling et al. [201]	See below[a]
Failure to rehydrate on IV	0.029	0-0.029	Hartling et al. [201]	
Phlebitis with IV	0.027	0-0.029	Hartling et al. [201]	
Paralytic ileus with ORT	0.027	0.027-0.04	Hartling et al. [201]	

a The Cochrane review reports that 0.065 patients fail to rehydrate on ORT. However, this review also reports 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 in those without paralytic ileus

(0.973 y) + (0.027 x 1.000) = 0.065

y = 0.039

The same method was carried out to derive the upper value of the range.

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 as a costing undertaken as part of this analysis was intended to capture the resource implications of the two treatment options.

* Derivations of the values used in the 'worst case' analysis are explained later in the paper.

Costs

There is variation in how oral rehydration and intravenous therapy 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 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 (staffing, equipment, consumables, 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)*[*]. 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 re-used. 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 given below:

$$E = \{K-[S/(1+r)^n]\}/A(n,r)$$

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 that which directly relates to rehydration therapy. For example, the 'hotel costs' associated with an inpatient admission.

ORT costing

ORT costs include staff and consumable costs only.

The patient population is defined by attendance at the emergency department (E.D). There are opportunity costs associated with an E.D attendance (administration, cleaning, bed changing etc.) over and above that relating directly to treatment. However, these opportunity costs do not vary by treatment method and can be excluded from the analysis.

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 E.D ; 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.

It is assumed that each patient receives an average of 2 sachets of Diarolyte for ORT.

[*] Compiled by Leslie Curtis

[†] 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.

No equipment is required for ORT treatment.

It is assumed that all children are discharged from A&E once they have received ORT

Table 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.

Table 3 ORT Labour Costs

Task (Staff)	Time taken (Range) (Minutes)	Unit cost	Cost (Range)	Source
Patient Education (Band 5 Nurse)	10 (10-20)	£30 per hour	£5.00 (£5.00-£10.00)	Units of Health and Social Care (2007)
Patient Review (Band 5 Nurse)	20 (20-30)	£30 per hour	£10.00 (£10.00-£15.00)	Units of Health and Social Care (2007)
Clinical Examination (Specialty Registrar)	10 (10-20)	£41per hour	£6.83 (£6.83-£13.67)	Units of Health and Social Care, (2007)
Total Labour Costs			£21.83 (£21.83-£38.66)	

Table 4 ORT Consumable costs

Variable	Quantity	Unit cost	Cost	Source
Diarolyte	2 sachets	£6.99 (20 sachet pack)	£0.70	BNF 55 (2008)
200ml bottles[a]	2 bottles	£11.50 (pack of 42)	£0.55	NHS Supply Chain (2007)
Total Consumable 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.

IVT Costing

Again E.D attendance costs are omitted from the costing of IVT (see ORT costing above),

All children on IVT are given approximately 500ml of Sodium Chloride 0.9% saline.*

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.

It is assumed that all children on IVT are admitted for in-patient stay where they complete IV treatment. We use the costs of 'Infection and Non Infectious Gastro without complications' (non-elective) as the HRG code for this admission.

Drip stands and infusion pumps are equipment pieces included in the costing of IVT. It is assumed that both of these are used for the 24 hour period of IVT.

* In practice, most children are given less than 500ml of saline. The smallest bag of saline available however, is of 500ml and once opened cannot be re-used. The cost used in the analysis therefore is that of a 500ml bag.

Baseline observations, equipment adjustments and site checks are assumed to be carried out hourly for the first 4 hours, i.e. during their time in the E.D. These are all carried out by a band 5 nurse.

Table 5 shows the range of time taken to carry out IVT related tasks and associated costs.

The in-patient stay is assumed to include any costs of further treatment during the patients stay in hospital. Table 7 shows the in-patient stay costs used in the analyses. The range of costs used for both base case and 'worst case' analysis is given in brackets

Table 5 IVT Labour Costs

Task (Staff)	Time taken (Range)	Number of times task is carried out	Unit cost	Costs (Range)	Source
Ametop application (Band 5 Nurse)	5 minutes (1-5 mins)	1	£30 per hour	£2.50 (£0.50-£2.50)	Units of Health and Social Care (2007)
Cannulation/taking bloods -2*Band 5 Nurse	Total of 35 minutes (0-35 mins)	1 1	£30 per hour	£17.50 (£0-£17.50)	Units of Health and Social Care (2007)
- Specialty Registrar	17.5 minutes (N/A)[a]		£41 per hour	£11.96 (N/A)	
Fluid preparation & attaching (2 * Band 5 Nurse)	Total of 15 minutes (10-15 mins)	1	£30 per hour	(£7.50) £5.00-£7.50	Units of Health and Social Care, (2007)
Base line observations (Band 5 Nurse)	10 minutes per hour (5-10 mins/hour)	4	£30 per hour	£20.00 (£10.00-£20.00)	Units of Health and Social Care (2007)
Equipment adjustment (Band 5 Nurse)	4 minutes per adjustment (N/A)	4	£30 per hour	£8.00 (N/A)	Units of Health and Social Care, (2007)
Site check (Band 5 Nurse)	5 minutes per check (N/A)	4	£30 per hour	£10.00 (N/A)	Units of Health and Social Care (2007)
Total Labour Costs				£77.46 (£45.46-£77.46)	

[a] These values did not vary between base case and 'worst case' analyses.

Table 6 IVT Consumable costs

Variable	Quantity	Unit cost	Cost	Source
IV Solution- Sodium Chloride (0.9% saline)	500ml	£1	£1	www.baxterheaalthcare.co.uk
Giving set with burette	2 (1 per 12 hours)	£1.75	£3.50	www.spservices.co.uk
Fluid Micron filter	1	£2.94	£2.94	NHS Supply Chain (2007)
Cannula	2	£0.78	£1.56	NHS Supply Chain (2007)
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)
0.9% Saline flushes	1*5ml vial	£0.33	£0.33	BNFC (2007)

Variable	Quantity	Unit cost	Cost	Source
Total Consumable Costs			£9.57	

Table 7 IVT Hospital Costs

Hospital Episode	Cost (Range)	Source
In-patient IV Stay	£602 (£365-£602)	Non elective In-patient HRG Data Reference Costs(2006/07)

Table 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.co.uk
Drip Stand	24 hours	5 years	£105.16	£0.29	www.midmeds.co.uk
Total Equipment Costs				£0.56	

Table 9: IVT Test Costs

Test	Quantity	Unit cost	Cost	Source
Full Blood Count and Diff	1	£2.71	£2.71	Pathology Indicative Tariff for Haemotology National Tarriff (2008/09)
Urea and Electrolytes	1	£2.71	£2.71	Pathology Indicative Tariff for Haemotology National Tarriff (2008/09)
Total Test Costs			£5.42	

Further IVT costing

It is assumed that if a child remains dehydrated after the initial 24 hours of IV therapy, treatment continues for another period of 24 hours. Patients receiving further treatment require additional resources. It is assumed that further IVT requires a longer inpatient stay. We have assumed 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 and without complications. This additional hospital stay is inclusive of any additional labour, consumable or equipment costs. Table 10 below summarises the hospital costs used in the analysis, the range of costs used for both base case and 'worst case' analysis are given in brackets.

Table 10 Further IVT Hospital Costs

Hospital Episode	Duration of stay	Cost Range	Source
Infectious & Non Infectious Gastro with complications	2 days	£820 (£489-£820)	Non elective In-patient HRG Data Reference Costs(2006/07)
Infectious & Non Infectious Gastro without complications	1 day	£602 (£365-£602)	Non elective In-patient HRG Data Reference Costs(2006/07)
In-patient Further IVT Stay	1 day	£218[a] (£124)	

[a] The 'Infectious & Non Infectious Gastro without complications' reference cost is for a 1day stay in hospital and in this model has been attributed to the inpatient stay costs for providing IVT. Similarly, the reference costs for 'Infectious & Non

Infectious Gastro with complications' is assumed to be the total costs for IVT and Further IVT. The value of £820 is therefore the costs 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 therefore in order to determine this cost, we deducted 'Infectious & Non Infectious Gastro without complications' from 'Infectious & Non Infectious Gastro 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 assumed that the majority of Phlebitis resolves after the removal of the cannula. The costs of Phlebitis are therefore attributed to the re-siteing of the cannula and all associated equipment and staffing costs. Potential antibiotic costs for the treatment have been excluded from the model. 'Extravisation' injuries as a result of Phlebitis have also been excluded from the model. The assumption 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 is encapsulated in the downstream cost of IVT and not as a separate cost.

Table 11 Phlebitis Costs

Item	Cost	Notes
Cannula	£0.78	
Staff Tasks: Ametop application Cannulation & taking bloods Fluid preparation / attaching	£8.42	It is assumed that re-siteing the cannula and associated tasks take approximately 15 minutes. These tasks are done by nurses (band 5) and a specialty registrar.

Table 12 NICE's willingness to pay for a QALY threshold

Item	Value	Source	Notes
Willingness to Pay	£20,000 per QALY	NICE Guidelines Manual	For threshold analysis

'Worst Case' Sensitivity Analysis

In addition to the base case analysis, a worst-case analysis for ORT relative to IVT has also been considered. This was done in order to subject the findings of the base case model – that ORT was most 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 estimate of proportions, the upper limit of the 95% confidence interval was 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 higher level of hospitalisation within ORT.

Staff

The GDG were asked estimated 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 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 and 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 relative low cost method of delivering IVT (see table 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 quartile for inpatient IV and further IV stay was used in order to keep the total costs of delivering IVT to the lowest possible value (see table 7).

Results

The results for the baseline and 'worst case' analysis are presented in Table 13 and 14 respectively.

Table 13 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		
IV	£701.56	£630.48	0.032

Table 14 '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		
IV	£426.01	£351.84	0.018

In Tables 13 and 14, the two strategies are ranked in terms of cost, least costly first. With both therapies it is assumed that all patients are hydrated within a given timeframe 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 13 and 14 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 provide 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 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 also presented in Table 12.

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.

Figure 4 shows one-way sensitivity analysis for the probability of phlebitis. This probability is ranged from 1-10% to illustrate how this changes the incremental costs of IVT. Figure 5 also shows one-way sensitivity analysis for the probability of paralytic ileus, again ranging from 1-10%. Finally, Figure 6 shows a one-way sensitivity analysis varying the costs of ORT, (although this can be considered equivalent to a sensitivity analysis varying the cost differential between ORT and IVT)

* For these analyses it is base case values that are kept constant

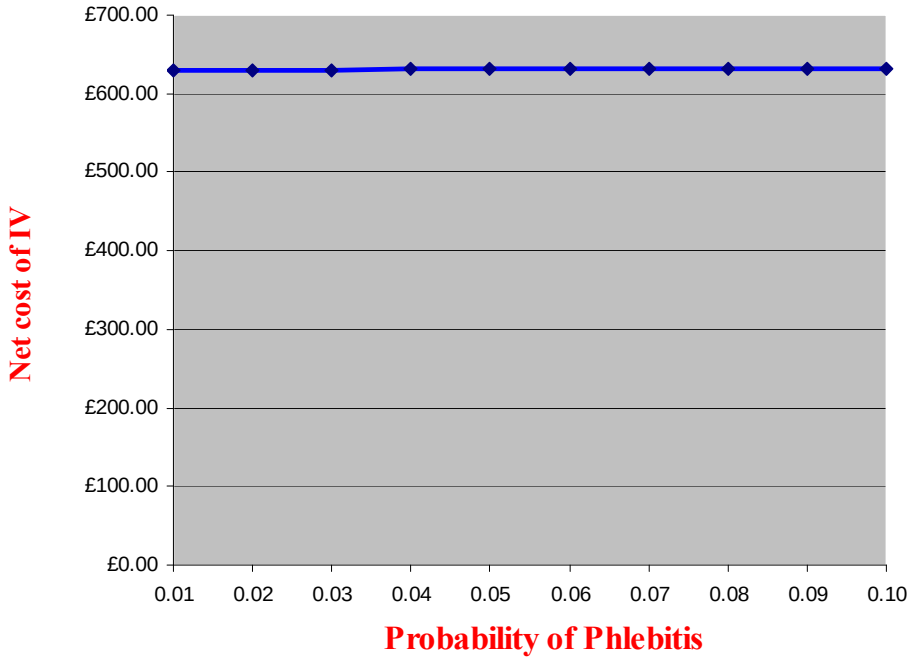


Figure 4 One way sensitivity analysis varying the probability of phlebitis as a complication of IVT

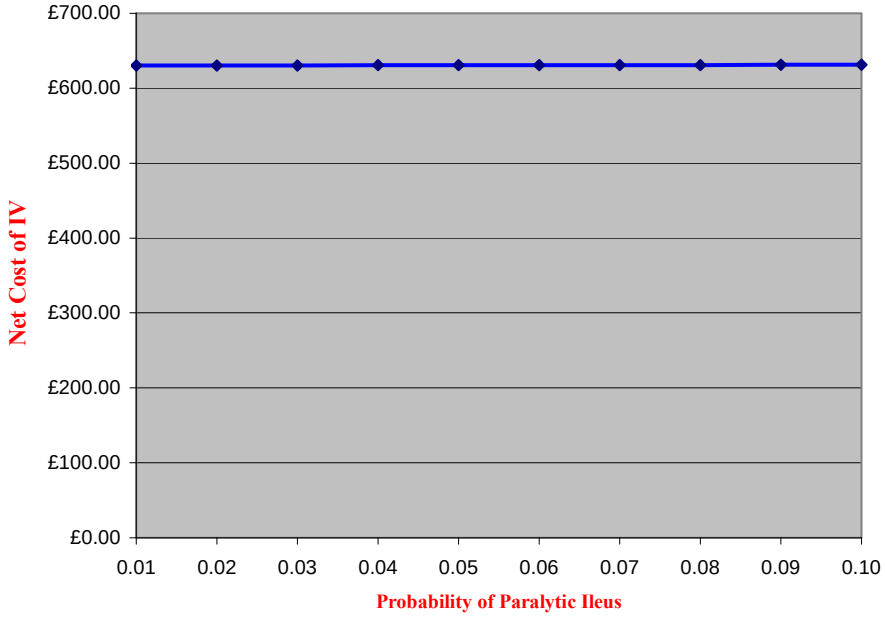


Figure 5 One way sensitivity analysis varying the probability of Paralytic Ileus

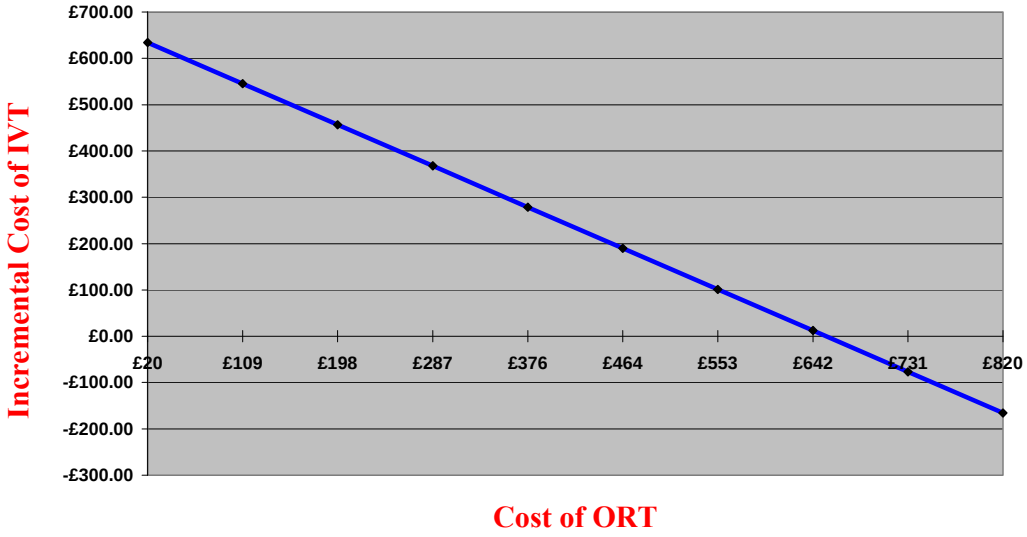


Figure 6 One way sensitivity analysis varying the differential in initial treatment costs.

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 probability distribution for some or all model parameters. A Monte Carlo simulation is then run which involves running the model many times each 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 whilst 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 7.

* Other model parameters are held constant as in the deterministic baseline analysis.

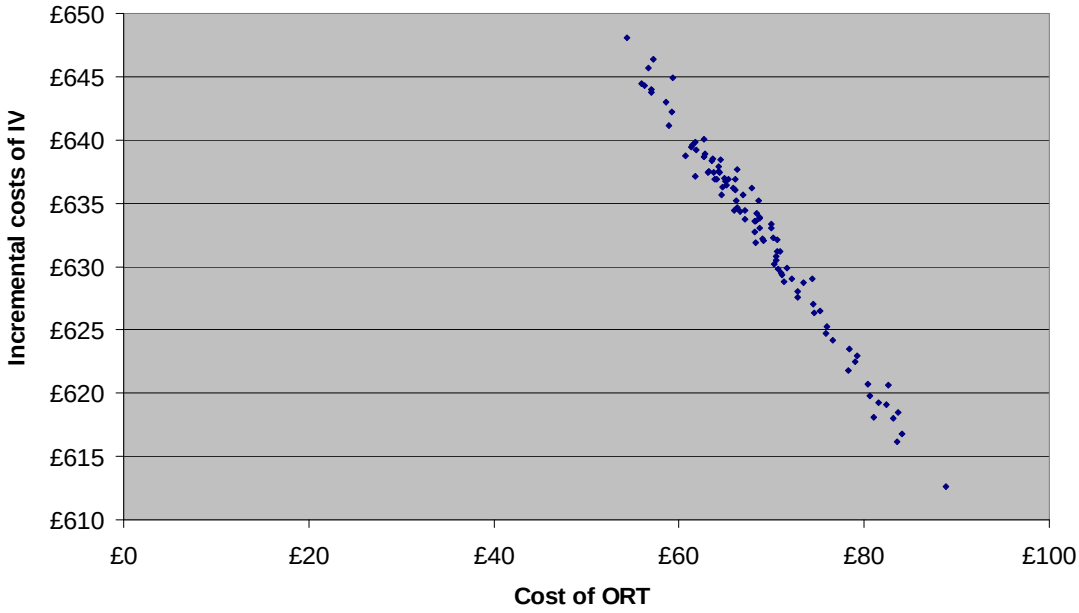


Figure 7 Monte Carlo simulation showing the cost of ORT against the incremental costs of IVT

In this analysis the probability of ORT being cheaper than IV was 100%.

Discussion

The baseline result shown in Table 13 suggests that, when "downstream" costs* are considered, ORT is £630.48 cheaper than IV. Table 14 shows that in the 'worst case' sensitivity analysis, ORT is £351.84 cheaper than IV.

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, whilst 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 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.

* Costs which are incurred as a result of the treatment but subsequent to it – e.g. costs arising from treatment complications

To allow for the possibility that the treatments are not equally efficacious the results in Table 13 and 14 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 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 one QALY. Hence, an intervention that gave an additional day of life lived in perfect health therefore would yield an incremental gain of 0.002 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 to dehydration is likely to be much less than one.

The sensitivity analysis illustrated in Figure 4 and 5 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 6, unsurprisingly shows 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 probabilistic sensitivity analysis in Figure 7 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). From the sampling, ORT may be more expensive if higher treatment failure values are sampled and/or higher rates of paralytic ileus. Similarly, the cost of IVT will depend 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 to be the most 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 for which there currently exists no established method of treatment. 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 intra-venous 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 therefore 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 used frequently in post-operative patients and also in oncology. The GDG felt that economic analysis would help guide recommendations regarding its use.

Economic analysis

A literature review identified several articles looking at the effectiveness of ondansetron in children with vomiting due to gastroenteritis. Evidence was for both oral and intra-venous uses of ondansetron. Due to limited evidence for the efficacy of intra-venous ondansetron the economic analysis only considers oral administration. None of the articles retrieved included any data regarding to costs or cost-effectiveness. A simple cost model was constructed to assess the cost-effectiveness of ondansetron.

Model probabilities are taken from a meta-analysis which pooled the results of 3 trials [159,163,164] that compared the effects of the administration of oral ondansetron against placebo in children with vomiting. The three main outcomes considered were:

- Cessation of vomiting
- Need for IV fluid therapy
- Hospitalisation.

Model costs are taken from the decision analytical model for the Cost effectiveness of ORT v IVT and are presented in Table 1. The cost for Ondansetron was obtained from the British National Formulary for Children (BNFC). It is assumed that only one dose of ondansetron (at a strength of 4mg) is given to the vomiting patient.

Table 1 Costs

Item	Value	Source
Ondansetron	£3.24	British National Formulary for Children (BNFC 2007)
IV treatment	£93.01	Cost Effectiveness of IV v ORT for children with mild to moderate dehydration (see Appendix X)
Hospitalisation	£602.00	Cost Effectiveness of IV v ORT for children with mild to moderate dehydration (see Appendix X)

The analysis calculates the difference in effect between placebo and ondansetron for the 3 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; the cost of ondansetron. Therefore:

Net savings = 'Downstream' savings - Treatment cost of ondansetron

Results

The results of the analysis can be seen in Tables 2 below. Note: The outcome of 'cessation of vomiting' was only reported in 2 of the trials (Freedman and Ramsook).

Table 2 Results of Pooled Analysis

Outcome	Control	Ondansetron	Difference in effect	Net savings with ondansetron
Cessation of vomiting	0.652	0.862	0.21	N/A*
Hospitalisation	0.099	0.039	0.06	£36.07
Need for IV treatment	0.137	0.339	0.20	£18.79
Total Net savings				£51.63

Discussion

The results of the pooled analysis (Table 2) show that giving a child a dose of ondansetron may lead to potential net savings of £51.63 when compared with no treatment. Similarly, the results of the individual trials, show net savings from the use of ondansetron. These savings are a result of reduced intra-venous therapy and consequently a reduction in hospital admissions.

There a number of caveats that need to be remembered when discussing the above results.

Firstly, two studies report the outcome of 'cessation of vomiting' occurring 'a few hours' after ondansetron is taken. Both studies have a different definition of what this time frame is. Freedman looks at the proportion of children who vomited whilst receiving ORT whereas Ramsook looks at the frequency of emesis during the 48 hrs period after enrolment. The important thing to note here is that if patients are continuing to vomit for a given time after taking ondansetron, they would not be kept in A&E for any longer than a total of 4 hours within the NHS. The child would need to be admitted for some kind of inpatient stay regardless to whether or not the child then goes onto receives IVT or is simply being kept at hospital to be monitored. This inpatient stay would therefore incur further costs. The evidence from US papers reflects the differing models of care between the US and the UK. In the US, children would be kept in the A&E for many hours (more than 4) and consequently sent home after monitoring or if needed, successful IVT.

The inclusion criteria for all three trials also varied. Freedman included children with at least one reported episode of vomiting within the 4 hours preceding triage whereas Ramsook enrolled patients with 5 episodes of vomiting in the preceding 24 hours. The authors felt that the inclusion criteria for those being given ondansetron should be high in order to best identify the group of patients who are going to benefit from ondansetron. This reinforces the view of the GDG who also agree that not every

* Vomiting has been assumed to have zero associated costs therefore zero savings are made by the cessation of vomiting.

child should be given ondansetron and the importance of giving ondansetron to those patients who are most likely to benefit, i.e. to those patients who would fail ORT and go onto IVT. It is for this group of patients that savings would be made.

None of the three above mentioned studies report any significant adverse events or complicating side effects from the use of ondansetron. The economic analysis has not taken into any account the effect of any possible side effects. However, the BNFC 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 result in a difference of quality of life between the two treatments. It is therefore important to remember the importance of any potential harms that may be of clinical importance and may differ systematically between the two treatment alternatives. The Ramsook and Freedman trials report an increased frequency of diarrhoea as an adverse event. It would be useful to know the clinical significance of diarrhoea and whether it led to concomitant increased use of health care resources.

In the economic model, it is assumed patients are given a single oral dose of ondansetron in order to reduce vomiting in the patient. This is in line with the Freedman and Roslund study. The Ramsook study gave a single oral dose of ondansetron in hospital but in addition to this, also provided discharged patients with an additional 5 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 deliver persistent benefit and consistently reduce hospital admission. This would change the results of the economic analysis. In addition to this, the analysis has also excluded any other treatment costs which may arise other than the cost of ondansetron itself e.g. staffing. This may also have an impact on the results of the analysis.

Although ORT has been proven to be a clinical 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, therefore a safe and effective method of controlling vomiting, such as ondansetron, may increase the use of ORT. A simple model is suggestive of potential clinical and economic benefits of ondansetron; however more evidence is needed 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: World Health Organization; 2007.
2. Bryce J, Boschi-Pinto C, Shibuya K *et al.* WHO estimates of the causes of death in children.[see comment]. *Lancet* 2005; 365:(9465)1147-52.
3. Kosek M, Bern C, and Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bulletin of the World Health Organisation* 2003; 81:(3)197-204.
4. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *Journal of Health Population and Nutrition* 2001; 19:(4)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:(3)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:(1)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:(8)1117-25.
9. The Pediatric ROTavirus European CommitTee (PROTECT). The paediatric burden of rotavirus disease in Europe. [66 refs]. *Epidemiology and Infection* 2006; 134:(5)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:(6)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:(7190)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:(5)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:(10)1827-34.
15. Bucher B and Aebi C. Population-based epidemiology of rotavirus hospitalisations in Switzerland. *Swiss Medical Weekly* 2006; 136:(45-46)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:(3)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:(2)132-42.
18. Duggan C, Santosham M, and 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* 1992; Recommendations and Reports. 41:(RR-16)1-20.
19. King CK. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR: Morbidity and Mortality Weekly Report* 2003; 52:(RR)1-16.
20. WHO. The Treatment of Diarrhoea – a manual for physicians and other senior health workers. No. 4th Edition. Geneva: World Health Organisation; 2005.
21. Bhatnagar S, Lodha R, Choudhury P *et al.* IAP Guidelines 2006 on management of acute diarrhea. [15 refs]. *Indian Pediatrics* 2007; 44:(5)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. Szajewska H, Hoekstra JH, and 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.[see comment]. *Journal of Pediatric Gastroenterology and Nutrition* 2000; 30:(5)522-7.
24. NHS Executive. Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS. London: HMSO; 1996.
25. National Institute for Health and Clinical Excellence. Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers. London: NICE; 2007.
26. Oxman AD, Sackett DL, and 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:(17)2093-5.

27. Guyatt GH, Sackett DL, and 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:(21)2598-601.

28. Guyatt GH, Sackett DL, and 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:(1)59-63.

29. Jaeschke R, Guyatt G, and 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:(5)389-91.

30. Jordan R and Law M. An appraisal of the efficacy and cost effectiveness of antenatal screening for hepatitis B. *Journal of Medical Screening* 1997; 4:(3)117-27.

31. Sackett DL, Straus SE, Richardson WS, Rosenberg W, and Haynes RB. Evidence-based medicine. How to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone; 2000.

32. Scottish Intercollegiate Guidelines Network. A guideline developers' handbook. No. 50. Edinburgh: SIGN; 2001.

33. Drummond MF, O'Brien B, Stoddart GL, and Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press; 1997.

34. Drummond MF, Sculpher M, Torrance GW, O'Brien BJ, and Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press; 2005.

35. Health Protection Agency. Guidance on Infection Control In Schools and other Child Care Settings. Health Protection Agency [online] 2006 [cited 2008 Dec 5]; Available from: URL:http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358374

36. 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.

37. Personal communication from Simon Minford, GDG member. 2008.

38. Guerrant RL, Van GT, Steiner TS *et al.* Practice guidelines for the management of infectious diarrhea. *Clinical Infectious Diseases* 2001; 32:(3)-351.

39. WHO. Diarrhoea treatment guidelines for clinical based healthcare workers. 2005. WHO.

40. Feldman M. Nausea and vomiting. In: Sleisenger MH, Fordtran JS, eds. Gastrointestinal disease: Pathophysiology, diagnosis, management. 4 ed. Philadelphia: W.B. Saunders Co.; 1989. p. 222-38.

41. 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:(2)247-53.

42. Gazala E, Weitzman S, Weizman Z *et al.* Early vs. late refeeding in acute infantile diarrhea. *Israel Journal of Medical Sciences* 1988; 24:(3)175-9.

43. Lozano JM and Cespedes JA. Lactose vs. lactose free regimen in children with acute diarrhoea: a randomized controlled trial. *Archivos Latinoamericanos de Nutricion* 1994; 44:(1)6-11.

44. 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:(2)193-8.

45. Khuffash FA, Sethi SK, and Shaltout AA. Acute gastroenteritis: clinical features according to etiologic agents. *Clinical Pediatrics* 1988; 27:(8)365-8.

46. 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:(5)417-9.

47. Dugdale A, Lovell S, Gibbs V *et al.* Refeeding after acute gastroenteritis: a controlled study. *Archives of Disease in Childhood* 1982; 57:(1)76-8.

48. Haque KN, al-Frayh A, and el-Rifai R. Is it necessary to regraduate milk after acute gastroenteritis in children? *Tropical and Geographical Medicine* 1983; 35:(4)369-73.

49. 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:(2)254-61.

50. Rees L and Brook CG. Gradual reintroduction of full-strength milk after acute gastroenteritis in children. *Lancet* 1979; 1:(8119)770-1.

51. Armitstead J, Kelly D, and Walker-Smith J. Evaluation of infant feeding in acute gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 1989; 8:(2)240-4.

52. Uhnoo I. Clinical features of acute gastroenteritis associated with rotavirus, enteric adenoviruses, and bacteria. *Archives of Disease in Childhood* 1986; 61:(8)732-8.

53. 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:(9)570-5.

54. Conway SP, Phillips RR, and Panday S. Admission to hospital with gastroenteritis. *Archives of Disease in Childhood* 1990; 65:(6)579-84.

55. 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:(2)177-85.

56. Cheney CP. Acute infectious diarrhea. *Medical Clinics of North America* 1993; 77:(5)1169-96.

57. Ellis ME. Contemporary gastroenteritis of infancy: clinical features and prehospital management. *British Medical Journal* 1984; 288:(6416)521-3.

58. Jenkins HR and Ansari BM. Management of gastroenteritis.[see comment]. *Archives of Disease in Childhood* 1990; 65:(9)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:(2)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:(3)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:(1)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. Health Protection Agency [online] 2008 Available from: URL:http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733811919?p=1191942150126

64. Travel and Migrant Health Section HPA. Foreign Travel-Associated Illness. England, Wales, and Northern Ireland. Annual Report 2005. 2005.

65. Borgnolo G, Barbone F, Guidobaldi G *et al.* C-reactive protein in viral and bacterial gastroenteritis in childhood. *Acta Paediatrica* 1996; 85:(6)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:(1)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:(9)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:(5)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:(2)160-4.

70. Zodpey 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:(4)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:(4)467-75.

72. Ahmed FU and Karim E. Children at risk of developing dehydration from diarrhoea: a case-control study. *Journal of Tropical Pediatrics* 2002; 48:(5)259-63.

73. Fuchs SC, Victora CG, and Martines J. Case-control study of risk of dehydrating diarrhoea in infants in vulnerable period after full weaning. *British Medical Journal* 1996; 313:(7054)391-4.

74. Steiner MJ, DeWalt DA, and Byerley JS. Is this child dehydrated? *JAMA: the journal of the American Medical Association* 2004; 291:(22)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:(6)2402-8.

76. World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources. 2005.

77. Sandhu BK and European Society of Pediatric Gastroenterology HaNWGoAD. Practical guidelines for the management of gastroenteritis in children. *Journal of Pediatric Gastroenterology and Nutrition* 2001; 33 Suppl 2:S36-S39.

78. Hill ID, Mann MD, and Bowie MD. Hypernatraemic dehydration. A prospective study in children with diarrhoeal disease. *South African Medical Journal* 1981; 59:(14)479-81.

79. Yurdakok K and Oran O. The relationship between blood glucose and serum electrolyte levels in children with acute diarrhea. *Turkish Journal of Pediatrics* 1992; 34:(3)145-52.

80. Reid SR and Losek JD. Hypoglycemia complicating dehydration in children with acute gastroenteritis. *Journal of Emergency Medicine* 2005; 29:(2)141-5.

81. Steiner MJ, Nager AL, and Wang VJ. Urine specific gravity and other urinary indices: inaccurate tests for dehydration. *Pediatric Emergency Care* 2007; 23:(5)298-303.

82. Faruque AS. Breast feeding and oral rehydration at home during diarrhoea to prevent dehydration. *Archives of Disease in Childhood* 1992; 67:(8)1027-9.

83. Hartling L. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. (Cochrane Review). In: Cochrane Database of Systematic Reviews, Issue 2, 2007. Chichester: Wiley Interscience.

84. Hidayat S and Srie Enggar KD. Nasogastric drip rehydration therapy in acute diarrhea with severe dehydration. *Paediatrica Indonesiana* 1988; 28:(3-4)79-84.

85. Sharifi J. Oral versus intravenous rehydration therapy in severe gastroenteritis. *Archives of Disease in Childhood* 1985; 60:(9)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:(1)28-33.

87. Wendland BE and 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:(5)564-6.

88. Duggan C, Fontaine O, Pierce NF *et al.* Scientific rationale for a change in the composition of oral rehydration solution.[see comment]. *JAMA: the journal of the American Medical Association* 2004; 291:(21)2628-31.

89. Hahn S, Kim Y, and Garner P. Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. *Cochrane Database of Systematic Reviews* 2007;(4).

90. Gavin N. Efficacy of glucose-based oral rehydration therapy. *Pediatrics* 1996; 98:(1)45-51.

91. Fontaine O, Gore SM, and Pierce NF. Rice-based oral rehydration solution for treating diarrhoea.[update in Cochrane Database Syst Rev. 1998;(4):CD001264; PMID: 17636662]. [23 refs]. *Cochrane Database of Systematic Reviews* 2000;(2)CD001264.

92. CHOICE Study Group. Multicenter, randomized, double-blind clinical trial to evaluate the efficacy and safety of a reduced osmolarity oral rehydration salts solution in children with acute watery diarrhea. *Pediatrics* 2001; 107:(4)613-8.

93. Sack DA, Islam S, and Brown KH. Oral therapy in children with cholera: a comparison of sucrose and glucose electrolyte solutions. *Journal of Pediatrics* 1980; 96:(1)20-5.

94. Santosham M. Glycine-based oral rehydration solution: reassessment of safety and efficacy. *Journal of Pediatrics* 1986; 109:(5)795-801.

95. Holliday MA and Segar WE. THE MAINTENANCE NEED FOR WATER IN PARENTERAL FLUID THERAPY. *Pediatrics* 1957; 19:(5)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. No. NPSA Safety Alert No. 9. London: National Patient Safety Agency; 2005.

97. Alam AN, Sarker SA, Molla AM *et al.* Hydrolysed wheat based oral rehydration solution for acute diarrhoea. *Archives of Disease in Childhood* 1987; 62:(5)440-4.

98. 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:(4)500-5.

99. Patra FC. Can acetate replace bicarbonate in oral rehydration solution for infantile diarrhoea? *Archives of Disease in Childhood* 1982; 57:(8)625-7.

100. Moenginah PA. Sucrose electrolyte solution for oral rehydration in diarrhea. *Journal of Tropical Pediatrics and Environmental Child Health* 1978; 24:(3)127-30.

101. Advanced Paediatric Life Support: The Practical Approach. 4th ed. BMJ Books / Blackwells; 2005.

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:(3)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:(5)343-8.

104. Reid SR and Bonadio WA. Outpatient rapid intravenous rehydration to correct dehydration and resolve vomiting in children with acute gastroenteritis. *Annals of Emergency Medicine* 1996; 28:(3)318-23.

105. Moineau G and Newman J. Rapid intravenous rehydration in the pediatric emergency department. *Pediatric Emergency Care* 1990; 6:(3)186-8.

106. Carcillo JA and Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Critical Care Medicine* 2002; 30:(6)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:(7153)235-40.

108. Wilkes MM and Navickis RJ. Patient Survival after Human Albumin Administration: A Meta-Analysis of Randomized, Controlled Trials. *Annals of Internal Medicine* 2001; 135:(3)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:(7162)882.

110. National Patient Safety Agency. Reducing the risk of hyponatraemia when administering intravenous infusions to children. No. NPSA/2007/22. London: National Patient Safety Agency; 2007.

111. Moritz ML. Prevention of hospital-acquired hyponatremia: A case for using isotonic saline. *Pediatrics* 111:(2)01.

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* 93:(4)Apr.

113. Skellett S. M. Chasing the base deficit: Hyperchloraemic acidosis following 0.9% saline fluid resuscitation. *Archives of Disease in Childhood* 83:(6)2000.

114. Hospital for Sick Children T. Emergency Department Rapid Intravenous Rehydration (RIVR) for Pediatric Gastroenteritis. Toronto; 2008.

115. Weaver L. Anatomy and Embryology. In: Walker WA, Durie PR, Hamilton RJ, Walker-Smith JA, Watkins JB, eds. Pediatric Gastrointestinal Disease. 2 ed. St Louis: Mosby; 1996.

116. Johnson JE and Sullivan PB. The management of acute diarrhoea. *Current Paediatrics* 2003; 13:(2)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:(6468)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:(5)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:(2)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:(3)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:(9)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:(8839)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:(9)936-8.

124. Ransome OJ and Roode H. Early introduction of milk feeds in acute infantile gastro-enteritis. A controlled study. *South African Medical Journal* 1984; Suid-Afrikaanse Tydskrif Vir Geneeskunde. 65:(4)127-8.

125. Conway SP and Ireson A. Acute gastroenteritis in well nourished infants: comparison of four feeding regimens. *Archives of Disease in Childhood* 1989; 64:(1)87-91.

126. Valois S. 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:(1)12-6.

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:(1 Pt 1)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:(7)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:(1)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:(2)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:(8)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:(5 Pt 1)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:(6)641-9.

135. Gabr M, Maraghi S, and 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, and Torrey S. Common clinical features as predictors of bacterial diarrhea in infants. *American Journal of Emergency Medicine* 1989; 7:(5)469-73.

137. Santosham M, Goepp J, Burns B *et al.* Role of a soy-based lactose-free formula in the outpatient management of diarrhea. *Pediatrics* 1991; 87:(5)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:(2)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:(1)46-51.

140. Casburn-Jones AC and Farthing MJG. Management of infectious diarrhoea. *Gut* 2004; 53:(2)296-305.

141. Nelson JD, Kusmiesz H, Jackson LH *et al.* Treatment of Salmonella gastroenteritis with ampicillin, amoxicillin, or placebo. *Pediatrics* 1980; 65:(6)1125-30.

142. Chiu CH, Lin TY, and 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:(4)372-4.

143. Kazemi M, Gumpert TG, and 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:(4)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:(3)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:(3)282-5.

146. 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:(2)355-60.

147. Pai CH, Gillis F, Tuomanen E *et al.* Erythromycin in treatment of Campylobacter enteritis in children. *American Journal of Diseases of Children* 1983; 137:(3)286-8.

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:(2)308-11.

149. 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:(3)717-25.

150. Wolfsdorf J and Myer EC. Trimethoprim-sulphonamide mixture in the treatment of infantile gastro-enteritis. *South African Medical Journal* 1973; 47:(40)1887-9.

151. 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:(4)886-90.

152. 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:(6)960-5.

153. Rodriguez RS, Chavez AZ, and 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.

154. De Bruyn G, Hahn S, and Borwick A. Antibiotic treatment for travellers' diarrhoea. *Cochrane Database of Systematic Reviews* 2000;(3)CD002242.

155. 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:(26)1930-6.

156. 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:(1)E12.

157. Lee WS, Puthucheary SD, and Boey CC. Non-typhoid Salmonella gastroenteritis. *Journal of Paediatrics and Child Health* 1998; 34:(4)387-90.

158. Nelson EA, Mok TC, and Yu LM. Retrospective comparison of management of gastro-enteritis in hospitalised children. *Annals of Tropical Paediatrics* 2002; 22:(2)165-71.

159. Roslund G, Hepps TS, and 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:(1)22-9.

160. 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:(10)1027-33.

161. British National Formulary 54. London: BMJ Publishing Group Ltd; RPS Publishing; 2007.

162. Cubeddu LX, Trujillo LM, Talmaciu I *et al.* Antiemetic activity of ondansetron in acute gastroenteritis. *Alimentary Pharmacology and Therapeutics* 1997; 11:(1)185-91.

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:(16)1698-705.

164. Ramsook C, Sahagun-Carreon 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:(4)397-403.

165. Watkinson M. A lack of therapeutic response to kaolin in acute childhood diarrhoea treated with glucose electrolyte solution. *Journal of Tropical Pediatrics* 1982; 28:(6)306-7.

166. 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:(3)424-6.

167. Szajewska H and Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. *Journal of Pediatric Gastroenterology and Nutrition* 2001; 33 Suppl 2:S17-S25.

168. 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:(7)463-7.

169. Cezard JP, Duhamel JF, Meyer M *et al.* Efficacy and tolerability of racecadotril in acute diarrhea in children. *Gastroenterology* 2001; 120:(4)799-805.

170. 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:(6)605-10.

171. 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:(23)1653-8.

172. 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:(1)18-27.

173. Li ST, Grossman DC, and Cummings P. Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis. *PLoS Medicine / Public Library of Science* 2007; 4:(3)e98.

174. 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:(3)605-10.

175. 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:(5)677-82.

176. 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:(13)839-44.

177. 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:(5)494-501.

178. 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:(11)1113-5.

179. Al-Sonboli N, Gurgel RQ, Shenkin A *et al.* Zinc supplementation in Brazilian children with acute diarrhoea. *Annals of Tropical Paediatrics* 2003; 23:(1)3-8.

180. 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.[see comment]. *Journal of Pediatric Gastroenterology and Nutrition* 2004; 38:(1)34-40.

181. Kronick JB. Immunization - Elimination of acute hepatitis B among adolescents after one decade of an immunization program targeting Grade 6 students: Commentary. *Paediatrics and Child Health* 2004; 9:(6)391.

182. 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:(4)311-9.

183. 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:(6)877-81.

184. 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:(5)898-903.

185. 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:(6)437-43.

186. 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:(7129)422-6.

187. Yurdakok K, Ozmert E, Yalcin SS *et al.* Vitamin A supplementation in acute diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 2000; 31:(3)234-7.

188. 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:(2)241-7.

189. Vanderhoof JA, Murray ND, Paule CL *et al.* Use of soy fiber in acute diarrhea in infants and toddlers. *Clinical Pediatrics* 1997; 36:(3)135-9.

190. Gorbach SL. The discovery of Lactobacillus GG. *Nutrition Today* 1996; 31:(6(suppl))2-4S.

191. Isolauri E. Probiotics for infectious diarrhoea. *Gut* 2003; 52:(3)436-7.

192. Allen SJ, Okoko B, Martinez E *et al.* Probiotics for treating infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2004;(2)CD003048.

193. Szajewska H. Probiotics and prebiotics in pediatrics: where are we now? *Turkish Journal of Pediatrics* 2007; 49:(3)231-44.

194. Szajewska H, Skorka A, and Dylag M. Meta-analysis: Saccharomyces boulardii for treating acute diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2007; 25:(3)257-64.

195. 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:(4)311-8.

196. 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:(2)e221-e228.

197. Salazar-Lindo E, Figueroa-Quintanilla D, Caciano 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:(5)571-6.

198. National Collaborating Centre for Women's and Children's Health. Feverish illness in children. Assessment and inital management in children younger than 5 years. 2007. London, RCOG Press.

199. Department of Health. National Service Framework for Children, Young People and Maternity Services - Core Standards. London: Department of Health; 2004.

200. Nager AL. Comparison of nasogastric and intravenous methods of rehydration in pediatric patients with acute dehydration. Pediatrics 2002; 109 (4):566-572

201. Hartling, L. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. Cochrane Database of Systematic Reviews (2). 2007