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European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe

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Background

The *ESPGHAN-ESPID Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe* are the outcome of an important task that the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has undertaken in collaboration with the European Society of Paediatric Infectious Diseases (ESPID). The collaboration was triggered by the understanding that acute gastroenteritis (AGE) is, still today and in all European countries, a major pediatric health problem. All children are expected to experience gastroenteritis in the first 3 years of age. Gastroenteritis is usually a mild disease in most European countries, but it is associated with a high number of hospital admissions and a not negligible number of deaths.

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Conflicts of interest of the members of the working group are listed at the end of the article.

Need for Guidelines

Europe encompasses a large number of wealthy and less wealthy countries that differ in tradition, culture, and health care systems. In Europe, management of diarrhea covers a broad range of interventions. In several countries, there is an excess of medical interventions in the attempt to reduce the intensity and duration of symptoms, which does not always result in clear beneficial outcomes. New options in terms of diagnosis, nutritional interventions, drugs, and now vaccines are becoming available, and may influence the severity and duration of symptoms and the rate of infection.

Clinical practice guidelines are an important tool to improve the quality and appropriateness of health care services. Many guidelines for AGE are available, but none of them include tables of evidence, which are the prerequisite for a state-of-the-art evidence-based document. Given these circumstances, ESPID and ESPGHAN jointly initiated an action to develop 2 parallel recommendation papers, one specifically targeted at rotavirus vaccination and the other with the broader target of the management of the child with AGE.

Guidelines Development Group

This project was strictly based on a thorough analysis of the evidence available, its evaluation, and the grading of statements and recommendations with specific instruments. The guidelines were developed by an ESPGHAN/ESPID Working Group that comprised 7 experts from France, The Netherlands, Israel, Italy, and Poland, coordinated by A.G. The experts are pediatricians with a special interest in gastroenterology and in infectious diseases. The work was undertaken as a collaborative research project: each working group member was in charge of systematically searching the literature, producing tables of evidence, and drafting the text. Specifically, the Naples group (A.G., F.A., A.L.) was in charge of the definition, epidemiology, risk factors, and indications for a medical visit and hospital admission; H.H. handled the clinical evaluation and disease severity section; R.S. and C.H. focused on diagnostic workup and nutritional management; the Warsaw group (A.C., B.P., M.R.) under the leadership of H.S. dealt with the methodological section, rehydration, and pharmacological therapy. Finally, the ESPID representatives (S.A., D.G.) were in charge of the anti-infective therapy and the prevention sections. The recommendations were formulated collectively, and the final draft was collated and harmonized in Naples, and was agreed upon by the entire working group. The final draft underwent external review and was approved by the ESPGHAN and ESPID councils.

Scope of Guidelines

The aim of these guidelines is to assist practitioners at all levels of health care—primary care physicians, pediatricians, and family physicians—in Europe while recognizing that each patient is unique. This document may be adapted for application in other areas in view of differences in organization of health care systems and local values and preferences (including cost). It also may assist local policymakers in deciding whether and how to manage AGE in young children based on local cost-effectiveness analysis.

Funding

Funding for both the evidence review and guideline development was provided through unrestricted educational grants from Merck Sharp & Dohme and GlaxoSmithKline. Although the sponsors were present during the meetings, none were involved in defining the methodology, scope, or content of the guidelines or in the formulation of individual recommendations.

The development of guidelines is only the first part of a complex process that includes dissemination of the information, the evaluation of efficacy and of applicability, and testing of their validity. These guidelines are in their first stage and need to be validated in their natural setting, Europe. They may help to reduce the enormous burden and consequences of gastroenteritis and may offer an interesting model of how to face a common childhood disease at a continental level.

Key Points

The main recommendations and conclusions emerging from this project are listed below:

1. Acute gastroenteritis is an extremely common problem in childhood, particularly in the first 3 years of life. In Europe, it is usually, although not always, a mild disease and death is an exceptional outcome. However, gastroenteritis is associated with a substantial number of hospitalizations and high costs.
2. The severity of gastroenteritis is related to etiology rather than to age, and rotavirus is responsible for the most severe cases.
3. Dehydration is the main clinical feature of AGE and generally reflects disease severity. Weight loss, prolonged capillary refill time, skin turgor, and abnormal respiratory pattern are the best individual clinical signs of dehydration.
4. Hospitalization should be reserved for children in need of procedures that can only be carried out in hospital, such as intravenous rehydration.
5. Microbiological investigations generally are not needed.
6. Rehydration is the key treatment and should be applied as soon as possible. Reduced or low osmolality oral rehydration solution should be used, and it should be offered ad libitum.
7. Regular feeding should not be interrupted and should be carried on after initial rehydration. Regular milk (lactose-containing) formulas are appropriate in the vast majority of cases.
8. Drugs are generally not necessary. However, selected probiotics may reduce the duration and intensity of symptoms. Other drugs may be effective but require further investigations.
9. Antibiotic therapy is not needed in most cases of AGE and may induce a carrier status in case of *Salmonella* infection. Antibiotic treatment is effective mainly in shigellosis and in the early stage of *Campylobacter* infection.
10. Prevention with antirotavirus vaccination is recommended for all children in Europe and is expected to consistently reduce the burden of gastroenteritis, and to prevent most of the severe cases, in the most susceptible age groups.

Methods for Guidelines Development

Defining the Clinical Questions

Development of clinical practice guidelines started with specifying clinical questions that defined the relevant population, type of intervention, comparison, and outcomes. The ESPGHAN/ESPID Working Group agreed, after discussion, on a list of clinical problems relevant to the management of acute infectious diarrhea and defined 1 question for each recommendation or set of recommendations. The clinical questions were grouped into the following categories: definition of diarrhea and epidemiology, risk factors for severe and/or persistent disease, clinical evaluation and disease severity, diagnostic workup, indications for medical visit and for hospital admission, rehydration, nutritional management, drugs and other therapies, and prevention.

Defining the Population for Search Purposes

The population for search purposes was defined as: previously healthy children 5 years old or younger with clinically diagnosed AGE (diarrhea presumably of infectious origin), in- or outpatients (principally children living in geographic Europe). However, it was not always possible to parse this age group in systematic reviews; therefore, in some cases, the data may include individuals up to age 18.

Searching for the Evidence

The evidence review procedures included section-specific targeted searches as well as formal systematic reviews on selected topics. The authors of each section of the guidelines were encouraged to conduct computerized literature searches to identify relevant literature in English; however, relevant papers in other languages also were considered in some instances. For the section-specific searches, the bibliographic databases, search terms, and selection procedures varied by topic, and are listed in Appendix 1. The data are presented in tables of evidence (see Appendix 2).

Strength of Evidence and Grade of Recommendations

The strength of evidence (1) and grades of recommendation (2) used in these guidelines are shown in Table 1. The strength of evidence is an objective measure that indicates the quality of the evidence on which a recommendation is based. Strength of evidence is graded from I to Vb, with I indicating the strongest type of evidence. The grade of recommendation is a qualitative indicator that considers the strength of evidence and such other factors as potential harm and costs relevant to an intervention when applied at individual or population level.

Recommendations were formulated and graded, and a consensus reached, after discussion during panel meetings of the working group. Any disagreement was resolved by discussion until the consensus was reached.

Finalizing and Harmonizing Recommendations

The draft of the guidelines was sent to all expert group members for review and further comments. All critical feedback was discussed and changes were incorporated as necessary.

External Review

A prefinal version of the document was sent for external review to experts in AGE to verify the completeness of the literature review and to ensure clinical sensibility. It also was sent to potential users. Their comments and suggestions were incorporated in the guidelines.

Open Peer Review

As part of the guideline development process, the preliminary conclusions and draft recommendations were presented at 2 international scientific meetings (the 40th Annual Meeting of ESPGHAN, Barcelona, Spain, 2007, and the 25th Annual Meeting of ESPID,

TABLE 1. *Strength of evidence and grade of recommendations*

	Strength of evidence		Grade of recommendation
I	Strong evidence from ≥1 systematic review of well-designed randomized controlled trials	A	Supported by level I evidence, highly recommended
II	Strong evidence from ≥1 properly designed randomized controlled trial of appropriate size	B	Supported by level II evidence, recommended
III	Evidence from well-designed trials without randomization, single group prepost, cohort, time series, or matched case-control studies	C	Supported by level III evidence; several potential clinical actions may be considered appropriate
IV	Evidence from well-designed trials, nonexperimental studies from >1 center or research group	D	Supported by level IV and V evidence; the consensus route would have to be adopted
Va	Opinions of respected authorities		
Vb	Clinical evidence, descriptive studies, or reports of expert committees		

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Porto, Portugal, 2007). Thus, the guideline development group obtained valuable feedback, suggestions for additional evidence, and possible alternative interpretations of some evidence. In addition, participants in the meetings were able to contribute to the final document, thereby generating a sense of ownership over the guidelines across geographical and disciplinary boundaries.

Updating the Recommendations

It is the intention of ESPGHAN and ESPID to revise the recommendations in 5 years and produce an updated document.

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DEFINITION

Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically $\geq$3 in 24 hours), with or without fever or vomiting. Diarrhea typically lasts less than 7 days and not longer than 14 days. However, a change in stool consistency vs previous stool consistency is more indicative of diarrhea than stool number, particularly in the first months of life.

The quantitative definition of AGE as ''3 or more loose or watery stools or any number of loose stools containing blood in a 24-hour period,'' validated in a prospective community-based surveillance study (1), has become the most widely accepted definition of AGE, and it is the one most often used in studies of incidence rates. However, this definition does not take account of age groups, or cultural or dietary features. Therefore, AGE should be defined in qualitative as well as quantitative terms, namely a change in stool consistency. Moreover, the definition should consider age because stool frequency is higher in infants below 3 months of age and may change depending on type of feeding. Information about the normal ranges of bowel movements of healthy children (2) can help to establish a definition of diarrhea according to age group. Stool volume is available only in a few clinical settings and cannot therefore be applied generally.

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EPIDEMIOLOGY

- The incidence of diarrhea ranges from 0.5 to 1.9 episodes per child per year in children younger than 3 years old in Europe.
- Rotavirus is the most frequent agent of acute gastroenteritis.
- The most common bacterial agent is either *Campylobacter* or *Salmonella* depending on country.

Few studies have examined the frequency of diarrheal agents in children in Europe. We identified 6 case-control studies of AGE-associated agents conducted in various European countries for at least 1 year in either the outpatient or inpatient setting for a total of approximately 2000 children under 5 years of age (1–6). Table 2 shows the ranges of frequencies of the main diarrheal agents reported in these studies. The geographical distribution of the main enteropathogens in European countries is shown in Figure 1.

In all 6 studies examined, AGE occurred most frequently between October and May, with a peak incidence between January and March. Most cases were due to viral infections, with rotavirus and norovirus being the most common agents. The peak incidence of rotavirus was between January and March, except in Sweden, where the incidences of AGE and rotavirus peaked slightly later (in April). The bacterial pathogens *Campylobacter jejuni* and *Salmonella* spp were diagnosed year round with

TABLE 2. *Frequency of enteropathogens in European children (0–5 y)*

Pathogen	Frequency, %
Rotavirus	10–35
Norovirus	2–20
Campylobacter	4–13
Adenovirus	2–10
Salmonella	5–8
EPEC	1–4.5
Yersinia	0.4–3
Giardia	0.9–3
Cryptosporidium	0–3
EAggEC	0–2
Shigella	0.3–1.4
STEC	0–3
ETEC	0–0.5
Entamoeba	0–4
No agent detected	45–60

EPEC = enteropathogenic *Escherichia coli*; EAggEC = enteroaggregative *E coli*; STEC = Shiga toxin–producing *E coli*; ETEC = enterotoxigenic strains of *E coli*.

FIG. 1. Geographical distribution of the main enteropathogens in European countries for which these data are available. The main agents of acute gastroenteritis (AGE) in European countries are listed in order of frequency. Rotavirus is the most common enteropathogen throughout Europe. *Campylobacter* is the second most frequent enteropathogen in northern countries, and *Salmonella* is in southern countries.

peaks in May to June and September to October. However, the incidence of enteropathogens is affected by climate and season.

Parasites are an infrequent cause of acute diarrhea in otherwise healthy children. The parasites that most often cause diarrhea in immunocompromised children or in children from low-income countries are *Cryptosporidium* and *Giardia*, and diarrhea tends to be chronic in both settings (7–11). In developed countries, parasites are most often seen in child care centers and nurseries, whereas in developing countries they are endemic and may contribute to malnutrition. *Isospora belli, Strongyloides stercoralis, Trichuris trichiura*, and *Entamoeba histolytica* also can cause diarrhea. Their importance varies depending on geographic location and the immune status of the child.

When AGE appears at a rate that substantially exceeds that expected in a given period in a given population, it is referred to as ''epidemic diarrhea.''

The estimated age-specific annual incidence rates for rotavirus gastroenteritis, which is the major cause of diarrhea in children, is consistently higher in children ages between 6 and 11 months and between 12 and 23 months than in any other age group, in all areas studied. *Campylobacter* is the most common enteropathogen after 5 years of age, particularly in North European countries. Table 3 shows the age-related pattern of the most common enteropathogens.

TABLE 3. *Age-related pattern of the most common enteropathogens*

<1 y	1–4 y	> 5 y
Rotavirus	Rotavirus	*Campylobacter*
Norovirus	Norovirus	*Salmonella*
Adenovirus	*Adenovirus*	Rotavirus
Salmonella	*Salmonella*	
	Campylobacter	
	Yersinia	

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RISK FACTORS FOR SEVERE AND/OR PERSISTENT DISEASE

The tables of evidence referring to the topics of this section can be found in Appendix 2, Tables 1.1 to 1.8.

Is There a Relationship Between Severe or Persistent Diarrhea and Clinical Features?

The severity of diarrhea is closely related to the grade of dehydration; vomiting should be considered an indirect sign of severe acute gastroenteritis, and should be carefully considered in the management.

Loss of appetite, fever, vomiting, and mucus in stools are frequently associated with persistent diarrhea (strength of evidence level III).

Moreover, fever and vomiting frequency of more than 2 episodes/day are common symptoms of rotavirus infection, which is considered the main cause of severe dehydrating diarrhea. These signs are frequent in children hospitalized for diarrhea (1). This observation confirms the results obtained in trials conducted in developing countries (2,3).

Is There a Relationship Between Severe or Persistent Diarrhea and Age?

The only study to assess age as a risk factor for severe diarrhea in Europe concluded that the high incidence of dehydration in infants younger than 6 months old is related to a higher exposure to rotavirus (III).

In developing countries, a young age (<6 months) was found to be related to the severity and persistence of diarrhea (II).

A prospective cohort study that examined a correlation between diarrhea severity and age in infants in Europe did not find any age-related differences in clinical features of diarrhea; however, the increased severity of diarrhea in infants and younger children appeared to be related to a higher exposure to rotavirus (4). There are no data about correlations between age and persistent diarrhea in industrialized countries. Children younger than 6 months of age in developing countries have a significantly higher risk for severe or persistent diarrhea episodes or death from diarrhea with respect to older children (5,6).

Is There a Relationship Between Severe or Persistent Diarrhea and Etiology?

Rotavirus, norovirus, astrovirus, enteroaggregative *Escherichia coli* and atypical *E coli* are the main pathogens detected in children with persistent diarrhea (III).

Rotavirus is the most severe enteric pathogen of childhood diarrhea (III).

In contrast to data from the developing world, viral pathogens play an important role in the etiology of persistent diarrhea in children in industrialized countries (7). Several studies demonstrate that rotavirus may be responsible for diarrheal episodes that, compared with those induced by other agents, are associated with higher severity scores, a higher number of vomiting episodes, and longer duration (8,9). European children with rotaviral gastroenteritis have a high risk of developing severe dehydration and of being hospitalized (4). Norovirus is the second most common enteropathogenic virus among children with gastroenteritis; it is considered a major cause of gastroenteritis in Europe (10). Among bacterial pathogens, enteroaggregative *E coli* and atypical *E coli* are related to persistent diarrhea episodes (7).

Is There a Relationship Between Severe or Persistent Diarrhea and Hospitalization?

There is no evidence that previous hospitalization can influence the severity or duration of diarrhea.

There is no direct evidence that nosocomial AGE is more severe than non-nosocomial AGE. However, nosocomial gastrointestinal infections led to a median estimated prolongation of hospitalization of 3 days.

Rotavirus is the main agent of nosocomial diarrhea. Duration of hospitalization, young age, presence of nonmedical individuals, and immunodeficiencies or malnutrition increase the risk of nosocomial rotavirus infection in children (9,11).

Is There a Relationship Between Severe or Persistent Diarrhea and Socioeconomic Factors?

In European countries, there is evidence, albeit weak, of a link between low socioeconomic status and the severity or persistence of diarrhea (III).

Two studies (7,12) show that the risk of persistent diarrhea is significantly higher for children who live with another person affected by diarrhea or with 3 or more people per room. These findings support the results obtained in developing countries (13–15). In addition, in industrialized countries, the following factors were found to be independently associated with an increased risk of diarrhea: recent travel abroad, contact with a symptomatic person, hospitalization, unemployment, and low educational status of parents (16,17). The major risk factor for viral diarrhea is contact with a symptomatic person in the past 2 weeks. The main risk factors for bacterial diarrhea are travel to countries in which there is a high risk of infective diarrhea and a low socioeconomic status.

Is There a Relationship Between Severe or Persistent Diarrhea and Feeding Practice?

There is evidence that breast-feeding reduces the rates of gastrointestinal infections in European children (III). There is little evidence that breast-feeding reduces the severity or duration of diarrhea in European children.

In developing countries, feeding practices are related to the severity and persistence of diarrhea: partially breast-fed, formula-fed, and early weaned children had a significantly higher risk for developing severe or persistent diarrhea compared with children who were exclusively breast-fed for longer times (5,18,19). The protective effect of breast milk against severe or persistent diarrhea may apply also to European children (12,20). A prospective study of a middle-class population demonstrated that breast-fed children have significantly fewer episodes of diarrhea and require less hospitalization than non- or partially breast-fed infants (21). The incidence of gastroenteritis was about 50% lower in breast-fed than in formula-fed children during the first year of life (22). Breast-fed infants were less likely to require hospital admission for gastrointestinal illness (23). In one study conducted in 1984, breast milk appeared to protect against rotavirus infection in younger infants (24). The duration of breast-feeding could be directly related to the protective effect of mother's milk. In fact, infants who were breast-fed for at least 3 months had substantially fewer gastrointestinal illnesses (12,23) and were significantly less likely to have an episode of diarrhea lasting 6 or more days (25,26).

Is There a Relationship Between Severe or Persistent Diarrhea and Day Care Attendance?

Children attending day care centers have a greater risk for mild and severe diarrheal illness compared with children cared for at home (III). No data are available for persistent diarrhea.

Admission to day care as a risk factor for common infections varies significantly with age (27). The highest incidence of diarrhea is found in children younger than 2 years (28,29). Microbiological analyses were not done in all studies, but a viral etiology seems to be the most frequent and probably justifies the age-related pattern. Rotavirus is the most frequent agent of acute gastroenteritis in day care centers, particularly in winter (8,28). In some geographic areas, sapovirus may be responsible for nearly 20% of viral cases (30).

Centers accepting children younger than 2 years have a high (>50%) risk of disease spread, which results in large outbreaks, whereas in centers accepting only children age 2 years or older the risk of spread is low (<10%) and outbreaks tend to be limited (31).

Is There a Relationship Between Severe or Persistent Diarrhea and Underlying Chronic Disease or Immune Deficiencies?

Children with immune deficiencies have a higher risk of developing chronic diarrheal episodes.

Children with congenital or acquired immune suppression have a higher incidence of recurrent infections. Such congenital immunodeficiencies as MHC-II deficiency and hypogammaglobulinemia and severe combined immunodeficiency syndromes are associated with an increased risk of chronic diarrhea, and the latter could represent the first manifestation of immunodeficiency (32,33). The average duration of diarrhea is often longer in immunodeficient than in healthy children. The major cause of acquired immune suppression, human immunodeficiency virus (HIV) infection, is the leading underlying condition associated with persistent diarrhea in developing countries. This association is explained by the limited access to effective antiretroviral therapies. Highly active antiretroviral therapy prevents HIV-related diarrhea. In European countries, there is no evidence linking HIV infection to either the severity or persistence of diarrheal episodes. This finding can probably be attributed to effective antiretroviral therapy.

In some African countries, there is a close association between chronic diarrhea and HIV, with the former

predicting the latter (34). There is no conclusive evidence of a relation between acquired immune deficiency syndrome (AIDS) and the risk for AGE or for its prolonged course. However, selected enteric agents, the so-called opportunistic pathogens, may be more frequent or more aggressive in HIV-infected children. The main opportunistic enteropathogen is *Cryptosporidium parvum*.

In the last several decades, with the widespread use of highly active antiretroviral therapy, severe or protracted diarrhea has become a rare event in children with AIDS. Other conditions such as malignancies or intestinal inflammatory diseases may expose children to severe diarrhea and require a specific approach.

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CLINICAL EVALUATION AND DISEASE SEVERITY

The tables of evidence referring to the topics of this section can be found in Appendix 2, Tables 2.1–2.2.

The incidence of various AGE-causing pathogens varies greatly among industrialized countries. The most

important factors governing the incidence of these pathogens are geographical localization, socio-economic situation, and season. Variations also may occur within the same country. When considering presenting symptoms the clinician has to take these differences into account. In this systematic review, the data were extracted from studies carried out in European countries in which there is a low prevalence of bacterial pathogens.

Is There a Single Clinical Feature That May Suggest a Bacterial versus Viral Etiology of Diarrhea?

High fever (>40°C), overt fecal blood, abdominal pain, and central nervous system (CNS) involvement each suggests a bacterial pathogen. Vomiting and respiratory symptoms are associated with a viral etiology (III, C).

Clinical research has focused on the following:

- Fever (different definitions of absent, low, moderate, and high)
- Vomiting (absent, present, and different definitions of frequent)
- Onset (abrupt or more gradual)
- Stool frequency (different definitions of low, moderate, and high)
- Fecal mucus (overt or not)
- Fecal blood (overt or occult)
- Abdominal pain (present or not)
- Respiratory symptoms (rhinorrhea, cough)
- CNS involvement (irritability, apathy, seizures, or coma)

In general, most of these symptoms are ill-defined or lack comparable outcome measures (1–10). Considered separately, each symptom has a low sensitivity and low-to-good specificity. The best predictors of etiology are listed below.

- Overt fecal blood is predictive of bacterial pathogens (1,3,5). Finkelstein et al (3) reported a positive predictive value (PPV) of 0.30 and a negative predictive value (NPV) of 0.91. Predictive values of overt blood are better in developing countries.
- High fever (>40°C) has a low PPV for a bacterial etiology, but a better NPV. High fever is common with *Shigella* (6). Moderate fever as a separate symptom will not help the clinician establish the etiology.
- Abdominal pain is moderately predictive of bacterial pathogens (1,5).
- CNS involvement is higher with bacterial pathogens, particularly *Shigella* and *Salmonella* (6).
- Respiratory symptoms are associated with viral pathogens. However, the association is related to seasonality rather than to pathogenic mechanisms of the virus (4,6).

There are no data about differences between parasitic and other groups of pathogens. Mixed infections with bacterial and viral pathogens cause more severe diarrhea than do infections with a single agent (5).

Are There Combinations of Clinical Features That May Suggest a Bacterial versus Viral Etiology of Diarrhea?

There is no evidence that combinations of clinical features can reliably predict a bacterial or a viral etiology.

Several investigators evaluated whether combinations of their more predictive symptoms and signs (3,11) or clinical scores (2) could increase the predictive values for bacterial pathogenesis. DeWitt et al (11) in a retrospective study found that an abrupt onset of diarrhea (>4 stools per day) and no vomiting before diarrhea onset delineated a subpopulation in which a bacterial etiology was more probable. Fontana (2) and Finkelstein (3) reported that fever plus overt fecal blood, and overt fecal blood plus high stool frequency ($\geq$10 stools/day) were more predictive of bacterial gastroenteritis than each item alone; however, the data are retrospective and further studies are required to verify this finding.

Are There Combinations of Clinical Features That May Suggest Different Viral Pathogens?

Clinical severity, vomiting, and dehydration are worse in rotavirus infections. Children with adenovirus 40/41 infections have less severe general symptoms. Vomiting is less prominent in astrovirus infections than in rotavirus infections (III, C).

Few studies have addressed clinical parameters as primary outcome. Data from case series are available for fever (not specified or graded) and general condition. Patients with adenovirus infections have less fever (5) and a better general condition (9) than children with rotavirus infection. Vomiting is less severe and lasts less in astroviral infection than in rotaviral infection (8,10). Similarly, clinical symptoms and dehydration are more severe in rotaviral infections than in astroviral infections (8). Only recently has norovirus been recognized as an important pathogen for AGE in young children, but data comparing clinical features with those induced by other viral pathogens are scarce. A case-control study on gastroenteritis within general practices in the Netherlands showed that young children with norovirus infection have important vomiting but less fever and diarrhea than children with rotavirus AGE (12).

Is This Child Dehydrated?

The best measure of dehydration is the percentage loss of body weight (Vb, D).

Classification into subgroups with no or minimal dehydration, mild or moderate dehydration, and severe dehydration is an essential basis for appropriate treatment (I, A).

In most cases the preillness weight is not available, but other criteria can provide an estimate of the degree of dehydration, as indicated below.

Inaccurate assessment of dehydration can have important consequences, namely a delay in administering urgent treatment, or overtreatment with unnecessary interventions. According to the World Health Organization (WHO) and the Centers for Disease Control (CDC) guidelines, patients are classified into subgroups for minimal or no dehydration (<3% loss of body weight), mild to moderate dehydration (3%–9% loss of body weight), and severe dehydration (>9% loss of body weight) (13,14). The first signs of dehydration will be apparent over a relatively wide range of fluid loss (from 3%–9% of body weight). Appropriate treatment is based on assessment of dehydration and classification into these subgroups. In daily practice, health care providers tend to overestimate the degree of dehydration (15).

How Can a Practitioner Assess Dehydration by Clinical History?

Parental reports on dehydration symptoms are so low in specificity that they may not be clinically useful. Parental report of normal urine output decreases the likelihood of dehydration (Vb, C).

In populations from industrialized countries, few data are available about the severity of diarrhea and/or vomiting and the amount of dehydration. In developing countries, infants and young children with frequent high output diarrhea and vomiting are most at risk (III, C).

In collecting the clinical history, the pediatrician will include recent weight measurements, the number of diapers (if appropriate), urine output, vomiting (amount and frequency), stools (amount and frequency), general condition, state of activity, whether the eyes appeared sunken, the amount of oral intakes including clear liquids at home, any changes from usual intake (less or increased), and temperature (16). Three studies evaluated low urine output as a predicting factor for dehydration (15,17,18). In the analysis of pooled data, the reported low urine output did not increase the likelihood of 5% dehydration (likelihood ratio [LR] 1.3; 95% confidence interval [CI] 0.9–1.9) (16). Parental report of normal urine output decreases the LR of dehydration to 0.27 (LR 0.27; 95% CI 0.14–0.51) (18). In developing countries, a high diarrhea output is reflected in the severity of dehydration (13). No data for European countries were found.

How Can a Practitioner Assess Dehydration Based on Signs and Symptoms?

Clinical tests for dehydration are imprecise, generally showing only fair to moderate agreement among examiners (III, C).

Historical points are moderately sensitive as a screening test for dehydration (III, C).

The best 3 individual examination signs for assessment of dehydration are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern (III, C).

The examination also will include assessment of overall appearance and alertness, respiratory rate, hyperpnea (deep, rapid breathing), temperature, pulse, and blood pressure. Skin turgor is assessed on the lateral abdominal wall at the level of the umbilicus. The fold elicited by the clinician's thumb and index finger will normally return instantly to normal after release (19,20). Excessive subcutaneous fat and hypernatremia may falsely lead to a normal turgor in dehydrated children, and malnutrition may falsely prolong the recoil time in moderately dehydrated subjects.

In general, the precision of examination signs and symptoms in assessing dehydration is low (16). The moderate agreement between parents and nurses and, not less important, the low rate of agreement among clinicians are other issues that should be taken into account.

Capillary refill time is measured on a finger with the arm at the level of the heart, in a warm environment. Pressure should be gradually increased on the palmar surface of the distal fingertip, then released immediately after blanching. The time to the reappearance of normal color is measured with a stopwatch. Values for nondehydrated children are less than 1.5 to 2 seconds (21). Reported biases are ambient temperature, site of application, lighting, medications, and primary or secondary autonomic changes (16).

Steiner et al (16) systematically reviewed the precision and accuracy of symptoms and signs for the evaluation of dehydration in young children (1 mo–5 y). Most children were from industrialized countries. The most useful signs for predicting 5% dehydration or more were an abnormal capillary refill time, abnormal skin turgor, and abnormal respiratory pattern. Cool extremities, a weak pulse, or absence of tears also may be helpful indicators of dehydration. Sunken eyes, dry mucous membranes, increased heart rate, a sunken fontanelle in young infants, and an overall poor appearance were less helpful in evaluating dehydration (Table 4).

What Is the Validity of Scores for the Assessment of Dehydration and Disease Severity?

Various scores have been proposed but they have not been validated for the assessment of dehydration in individual patients.

TABLE 4. *Summary test characteristics for clinical findings to detect 5% dehydration (16)*

Finding	Reference	Total no. of participants	LR summary value (95% CI) or range		Sensitivity (95% CI)	Specificity (95% CI)
			Present	Absent		
Prolonged capillary refill	(15,18,21,26)	478	4.1 (1.7–9.8)	0.57 (0.39–0.82)	0.60 (0.29–0.91)	0.85 (0.72–0.98)
Abnormal skin turgor	(15,18–20,26)	602	2.5 (1.5–4.2)	0.66 (0.57–0.75)	0.58 (0.40–0.75)	0.76 (0.59–0.93)
Abnormal respiratory pattern	(15,18,20,26)	581	2.0 (1.5–2.7)	0.76 (0.62–0.88)	0.43 (0.31–0.55)	0.79 (0.72–0.86)
Sunken eyes	(15,17,18,20)	533	1.7 (1.1–2.5)	0.49 (0.38–0.63)	0.75 (0.62–0.88)	0.52 (0.22–0.81)
Dry mucous membranes	(15,17,18,20)	533	1.7 (1.1–2.6)	0.41 (0.21–0.79)	0.86 (0.80–0.92)	0.44 (0.13–0.74)
Cool extremity	(17,20)	206	1.5, 18.8	0.89, 0.97	0.10, 0.11	0.93, 1.00
Weak pulse	(18,20)	360	3.1, 7.2	0.66, 0.96	0.04, 0.25	0.86, 1.00
Absent tears	(15,17,18)	398	2.3 (0.9–5.8)	0.54 (0.26–1.13)	0.63 (0.42–0.84)	0.68 (0.43–0.94)
Increased heart rate	(15,18,20)	462	1.3 (0.8–2.0)	0.82 (0.64–1.05)	0.52 (0.44–0.60)	0.58 (0.33–0.82)
Sunken fontanelle	(15,17,20)	308	0.9 (0.6–1.3)	1.12 (0.82–1.54)	0.49 (0.37–0.60)	0.54 (0.22–0.87)
Poor overall appearance	(15,17,18)	398	1.9 (0.97–3.8)	0.46 (0.34–0.61)	0.80 (0.57–1.04)	0.45 (−0.1 to 1.02)

LR = likelihood ratio; CI = confidence interval.

There is no proof to support the use of scoring system for the management of the individual child (Vb D).

In general, the severity of AGE is reflected by the degree of dehydration. When a clinical practitioner investigates a child at risk of dehydration, it may appear that combining relevant symptoms and signs (Table 4) would improve diagnostic power, but this has yet to be demonstrated. Various severity scores have been devised to evaluate dehydration. Friedman et al (22) grouped 4 items into a scale to evaluate the response to therapy in children with an established diagnosis of dehydration; however, the purpose of this study was not to diagnose dehydration. Fortin et al (23) proposed a dehydration scoring system for infants in developing countries. Only a few studies reported using this score, and none were carried out in developed countries. The so-called Ruuska-Vesikari 20-point score (24), initially developed to study the efficacy of rotavirus vaccination, also has been used to investigate the severity of rotavirus infection in a recent study performed in a European country (25). However, there are no data on any score system for the management of the individual child.

We support the use of scoring systems to assess dehydration; however, they may be difficult and cumbersome to apply in a single patient.

General Conclusions

The signs of dehydration can be imprecise and inaccurate, so that it is difficult to determine the exact degree of dehydration. In clinical practice, a physical examination enables the clinician to classify patients into the 3 groups of none, mild/moderate, or severe dehydration. This general assessment can then be used to guide clinical management.

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DIAGNOSTIC WORKUP

The tables of evidence referring to the topics of this section can be found in Appendix 2, Tables 3.1–3.3.

Are Microbiological Investigations Useful in Children With AGE?

- Stool cultures should not be routinely performed in children with AGE (Vb, D).
- Stool cultures and stool examination should be considered in cases of persistent diarrhea when antimicrobial treatment is envisaged (in case of an immunocompromised host or dysentery), when intestinal infection must be excluded to verify another etiology such as inflammatory bowel disease, and in case of an outbreak (Vb, D).

With a yield as low as 2% and a high cost per positive result, routine stool cultures are considered the most expensive and least useful microbiological tests. Children with AGE should not routinely undergo microbiological examination for a variety of reasons:

- An enteric agent is seldom identified. Although most diarrhea-associated pathogens are viruses, no likely pathogens have been identified in the majority of episodes in outpatients and inpatients (1–4).
- The results are available after 2 to 3 days, at which time symptoms have usually improved and most therapeutic decisions already have been made (5,6).
- The test costs between US$900 and US$1500 [corresponding to €680–1100] for 1 positive culture (5).
- The presence of healthy carriers of enteric agents complicates the interpretation of the results.

Moreover, prospective studies showed that diagnosis of bacterial diarrhea based on clinical features had a PPV and NPV of 75% to 86% and 60% to 71%, respectively (3,7,8). This means that clinical judgment based on the assessment of risk factors can be relied upon in deciding about the need for culture or antibiotic therapy, which, however, is only seldom needed even for bacterial diarrhea. With a combination of clinical features and positive stool leukocytes, sensitivity increased to 74% and specificity to 94%, PPV 69%, and NPV 95% (8).

A number of retrospective studies conducted in hospitalized children showed that isolation of a bacterial pathogen from the stool of children with onset of diarrhea beyond the third hospital day is a rare event, and that bacterial stool culture should not be a part of the initial evaluation of children with nosocomial diarrhea (6,9,10). Rotavirus and *Clostridium difficile* toxin tests have been shown to have a greater yield in this nosocomial population (6).

A body of data has helped to rationalize the use of stool cultures. Multivariate analyses performed in 4 prospective cohort studies of hospitalized and outpatient children showed a significant association between positive bacterial culture and passage of more than 10 stools in the previous 24 hours (relative risk [RR] 4.5) (2,3), travel to countries that have an increased risk of bacterial or parasitic infection (RR 3.7) (3), fever (RR 2.3) (3), older age (RR 1.2) (3), blood or mucus in stool ($P < 0.001$ and $P < 0.01$, respectively) (1,2,11), and abdominal pain ($P < 0.001$) (1). Consequently, stool culture is indicated in such cases.

Stool cultures and stool examination also should be considered in cases of persistent diarrhea, when a specific antimicrobial treatment is envisaged (eg, in case of dysentery), or when an intestinal infection must be excluded in order to support another etiology (eg, inflammatory bowel disease).

Is There Any Reliable Hematological Marker of Bacterial Diarrhea?

There is no hematologic marker that reliably differentiates between bacterial and nonbacterial AGE (Vb, D).

Although hematological data do not reliably differentiate between bacterial and nonbacterial AGE, some

TABLE 5. *Pooled analyses of rapid stool tests, by epidemiological setting*

	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR−	AUC/SROC
Developed countries					
Stool leukocytes	0.73 (0.33–0.94)	0.84 (0.50–0.96)	4.56	0.32	0.89
Fecal occult blood	0.71 (0.36–0.91)	0.79 (0.40–0.96)	3.38	0.37	0.81
Fecal lactoferrin	0.92 (0.67–0.99)	0.79 (0.74–0.82)	4.33	0.10	
Developing countries					
Stool leukocytes	0.50 (0.33–0.67)	0.83 (0.74–0.89)	2.94	0.60	0.79
Fecal occult blood	0.44 (0.32–0.57)	0.72 (0.60–0.82)	1.57	0.78	0.63
Fecal lactoferrin	0.95 (0.48–1.00)	0.29 (0.17–0.46)	1.34	0.17	0.60

CI = confidence interval; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; AUC/SROC = area under the curve/summary receiver operating characteristic (19).

markers can provide indications in clinical practice. In fact, whereas retrospective studies showed that white blood cell counts were of little value in differentiating bacterial from nonbacterial gastroenteritis, the absolute band count, and even moreso the band/neutrophils ratio, were found to be more powerful in distinguishing between bacterial and nonbacterial diarrhea (12–14). The only retrospective study that evaluated the yield from white blood cell counts found that in children with AGE, white blood cell band counts $>100/mm^3$ had a 100% sensitivity, 79% specificity, 9% PPV, and 100% NPV in identifying patients with positive stool culture (5).

The value of C-reactive protein and erythrocyte sedimentation rate measurement in predicting a positive bacterial stool culture has been determined in several prospective case-controlled cohort studies (15–17). At a cutoff >12 mg/dL, C-reactive protein had a 77% sensitivity, 89% specificity, 91% PPV, 72% NPV, odds ratio (OR) 25.8 (95% CI 7.58 to 87.93), and a receiver operating characteristic curve of 0.83. Erythrocyte sedimentation rate has been found to have lower sensitivity and specificity, and serum procalcitonin was more specific but less sensitive in distinguishing between a bacterial and nonbacterial etiology (15–17).

Can Any Stool Marker Differentiate a Bacterial From a Nonbacterial Agent?

At present, we cannot recommend the routine use of any stool assay.

In 1996, Huicho et al (18) examined 25 studies (adults and children) to determine the value of stool leukocytes, fecal occult blood, and fecal lactoferrin in the work-up of patients as screening tests in the approach to acute diarrhea (identification of bacterial etiology and institution of targeted antimicrobial therapy). Fecal lactoferrin was the most accurate index test, and fecal leukocytes showed the lowest performance as assessed by the area under the curve. Occult blood yielded intermediate curves. More recently, a meta-analysis examined the diagnostic accuracy of rapid stool assays in AGE (19). The analysis of data pooled from 15 studies and 7161 children and adults from developed and resource-poor countries is shown in Table 5.

In conclusion, in developed countries tests for fecal leukocytes, occult blood, and lactoferrin were moderately useful and could identify patients who were more likely to benefit from antibiotic therapy, whereas in developing countries rapid stool assays performed poorly. However, only 1 trial of fecal lactoferrin came from developed countries, and it involved only adult patients. No studies on the subject appeared after 2003. There are no data on fecal calprotectin in AGE in either children or adults.

Is Endoscopy and/or Histology Useful for the Management of Children With AGE?

There is no indication for endoscopy except in selected circumstances or cases (Vb, D).

No study has prospectively evaluated the diagnostic value/yield of endoscopy and mucosal histology in the diagnosis of AGE in children. Several descriptive retrospective and prospective studies have been undertaken to determine the natural history of self-limited infectious colitis in adults and to evaluate if endoscopic or histological parameters quickly and reliably differentiate between self-infective colitis and inflammatory bowel disease. Histopathology was found to be a reliable tool for the rapid differentiation of acute self-limiting colitis from ulcerative colitis in a few clinical case reports of intestinal infection, inflammatory bowel disease, or surgical conditions. Endoscopy should be considered in these cases. However, the biopsy specimens were diagnostic only when obtained during the acute phase of illness, namely usually within the first 4 days of the onset of symptoms (20–25).

Does Any Biochemical Test Change the Approach to the Child With Gastroenteritis?

Biochemistry

Tests of dehydration are imprecise, and generally there is only fair to moderate agreement among examiners.

Historical points are moderately sensitive as a screening test for dehydration (III, C).

The only laboratory measurement that appears to be useful in decreasing the likelihood of >5% dehydration is serum bicarbonate (normal serum bicarbonate) (III, C).

Electrolytes should be measured:

- In moderately dehydrated children whose history and physical examination findings are inconsistent with a straight diarrheal disease, and in all severely dehydrated children (Va, D).
- In all children starting intravenous (IV) therapy, and during therapy, because hyper- or hyponatremia will alter the rate at which IV rehydration fluids will be given (Va, D).

An American Academy of Pediatrics practice parameter notes that most episodes of dehydration caused by acute diarrhea are isonatremic, and serum electrolyte determination is unnecessary (26). However, it also was stated that electrolytes should be measured in moderately dehydrated children whose history and physical findings are inconsistent with straight diarrheal disease (namely, when no other diagnosis is suspected, such as ileus, systemic, metabolic, or endocrine disease) and in all severely dehydrated children. Electrolytes should be measured in all children who start receiving IV therapy and as therapy continues, because hyper- or hyponatremia will alter the rate at which IV rehydration fluids will be given.

In a prospective multicenter study, Rothrock et al (27) looked for criteria to identify children who present to the emergency department with clinically significant electrolyte abnormalities. They found that the presence of 6 criteria (age <6 months; dry mucus membranes, vomiting, delayed capillary refill, absence of diabetes mellitus, and tachycardia; each of which had OR 115 [95% CI 7.1 to 1860]) identified all children with clinically significant electrolyte abnormalities. If these criteria had been used to order electrolyte panels, no clinically significant electrolyte abnormality would have been missed, and 18% of the electrolyte tests could have been avoided.

There is no consensus about the value of conventionally applied laboratory criteria (serum blood urea nitrogen [BUN], base excess or pH, serum electrolyte panel) as predictors of the degree of dehydration (28–34). Some studies suggest that serum urea greater than 100 mg/dL (35) and a serum bicarbonate concentration of 13 mEq/L or less (34–36) can be helpful in the estimation of fluid deficit regardless of serum sodium concentration. Moreover, only a few children benefit from a change in treatment based on laboratory results. Steiner et al (37) reviewed 13 studies. The difference between the rehydration weight and the acute weight divided by the rehydration weight was selected as the best available gold standard for calculation of the percentage of volume loss. Only 6 of the 13 studies evaluated the effectiveness of laboratory tests in assessing dehydration (28,29,31,32, 35,38).

Five of the studies evaluated BUN concentration or the BUN/creatinine ratio as a test for dehydration. BUN cutoffs of 8, 18, and 27 mg/dL produced LRs ranging from 1.4 to 2.9. A single, small study found that BUN >45 mg/dL had a 100% specificity for diagnosing greater than 5% dehydration (35). Four studies evaluated acidosis as a test for dehydration. Some studies used base deficit; others used serum bicarbonate concentration at different cut-off values. Base deficit showed LRs <2, whereas an absolute serum bicarbonate value of less than 17 mEq/L was of some help (LR 3.5; CI 2.1–5.8). Serum uric acid concentration, increased anion gap (29) and urine specific gravity (39) were not helpful. The only laboratory measurement that appeared to be useful in decreasing the likelihood of >5% dehydration was serum bicarbonate. A serum bicarbonate level of more than 15 or 17 mEq/L has an LR range between 0.18 and 0.22 of reducing the likelihood of dehydration if the child has AGE.

None of the clinical or laboratory variables has a significant statistic or clinical association with a severe outcome of AGE. Some studies suggest that serum urea greater than 100 mg/dL (35) and a serum bicarbonate concentration of 13 mEq/L (34,36) can be helpful in the estimation of fluid deficit regardless of serum sodium concentration.

The evidence shows that tests of dehydration are imprecise, and generally there is only fair to moderate agreement among examiners. Historical points are moderately sensitive as a screening test for dehydration.

The prevalence of hypoglycemia in children with AGE has been estimated to be between 1.9% and 9.2% (40–43) and up to 13.6% in infants less than 3 months (44). The only prospective study that evaluated the prevalence and risk factors associated with hypoglycemia in children with AGE showed that female gender (OR 2.6; 95% CI 1.3–5.0), signs of neuroglycopenia (the lack of adequate glucose supply to the central nervous system) ($P = 0.007$; OR 3.5; 95% CI 1.4–8.6), and more or an equal number of vomiting episodes to diarrhea episodes ($P = 0.046$; OR 2.1; 95% CI 1.0–4.4) were predictors of hypoglycemia. The presence of 1 of the 3 variables had a sensitivity of 67% and a specificity of 71% for detecting hypoglycemia. Neuroglycopenia in a female or in the presence of vomiting had a sensitivity of 68% and specificity 69% for detecting hypoglycemia. The clinical variables investigated in the study were not shown to be sufficiently sensitive and specific to allow clinicians to accurately predict which children with AGE

and dehydration have hypoglycemia. Because the potential consequences of untreated hypoglycemia are substantial, clinicians should maintain a low threshold for measuring serum glucose in children younger than 5 years with AGE and dehydration.

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INDICATIONS FOR A MEDICAL VISIT AND FOR HOSPITAL ADMISSION

The table of evidence referring to the topic of this section can be found in Appendix 2, Table 4.1.

What Are the Indications for a Medical Visit?

A telephone consultation can be appropriate in the management of a child with gastroenteritis in uncomplicated cases (Vb, D).

Infants and toddlers with AGE should be referred for medical evaluation if any of the following are present:

- High output diarrhea with substantial stool volumes (>8 episodes/day) (III, C)
- Persistent vomiting (III, C)
- Severe underlying disease (eg, diabetes and renal failure) (Vb, D)
- Age younger than 2 months (III, C).

Acute gastroenteritis in European countries is generally a relatively mild and self-limiting condition that may be managed at home, but it may occasionally evolve into a serious illness. Treatment of diarrhea should begin at home. Families should be encouraged to have a supply of oral rehydration solution (ORS) at home at all times and to start rehydration as soon as diarrhea begins, regardless of the etiologic agent. Early administration of ORS can reduce complications, and reduce the number of office, clinic, and emergency department visits and hospitalizations (1–3).

A telephone consultation can be appropriate in the management of a child with gastroenteritis in uncomplicated cases. The physician can elicit relatively sound information about the child's clinical condition by asking the caregiver (if he or she is known to be reliable) clear, specific, easy-to-understand questions.

Questions to caregivers should focus on factors that are related to risk of dehydration:

- Child's age
- How long (hours or days) has the child been ill
- The number of episodes of diarrhea or vomiting, and the approximate amount of fluids lost
- Urine output
- The child's neurological condition (lethargy, etc).

The physician also should ask questions about the child's remote and recent medical history, and whether the child has been exposed to possible sources of infection. Caregivers also can be taught to recognize signs of illness or treatment failure that necessitate medical intervention.

No guidelines have established a specific age under which evaluation is mandated, but young age (2–3 months) is an indication for medical evaluation. In fact, several case-control studies (4–7) concluded that children in the first 2 to 3 months of life are relatively protected from developing diarrhea, but once diarrhea occurs, they have a higher rate of dehydration and complications compared with infants ages 9 to 11 months.

What Are the Indications for Hospitalization?

There are no established admission criteria for gastroenteritis. It is impossible to perform case-controlled studies for ethical reasons. Overall, in developed communities many children who are not severely dehydrated are admitted to hospital and receive unnecessary intravenous fluids (8–10).

The recommendations for hospital admission are based on consensus and include any of the followings conditions (Vb, D):

- Shock
- Severe dehydration (>9% of body weight)
- Neurological abnormalities (lethargy, seizures, etc)
- Intractable or bilious vomiting
- ORS treatment failure
- Caregivers cannot provide adequate care at home and/or there are social or logistical concerns
- Suspected surgical condition

What Isolation Precautions Are Indicated for a Child With Gastroenteritis?

For acute diarrhea with a likely infectious cause, contact precautions are advised in addition to standard precautions (11).

Standard Precautions

- Hand hygiene: After touching blood, body fluids or contaminated items; immediately after removing gloves; between patient contacts
- Personal protective equipment
  - Gloves: for touching blood, body fluids, nonintact skin or mucous membranes, etc.
  - Gown: during procedures and patient care activities when contact of clothing/exposed skin with blood/body fluids, secretions, and excretions is anticipated
  - Mask, eye protection, face shield: During procedures and patient care activities likely to generate splashes or sprays of blood, body fluids, or secretions
- Soiled patient-care equipment: Handle in a manner that prevents transfer of microorganisms to other people or to the environment
- Environmental control: Develop procedures for routine care, cleaning, and disinfection of environmental surfaces

- Textiles and laundry: Handle in a manner that prevents transfer of microorganisms to others and the environment
- Correct injection practices: Do not recap or hand-manipulate used needles; use a needle-free safety device when available; place used sharps in a puncture-resistant container.
- Adequate patient placement: Prioritize for single-patient room if patient is at increased risk of transmission.

Contact Precautions

- If possible, single-patient room (for patients who do not control body excretions)
- Gloves (nonsterile)
- Hand hygiene after glove removal
- Gowns after direct contact with a patient, surface, or items in the patient's room.
- Gowns should be removed before leaving the patient's room

Cohorting is discouraged, even if based on etiology, because of the risk of harboring multiple agents that may worsen the disease.

When to Discharge a Child Admitted Because of Gastroenteritis

As suggested by the Cincinnati Children's Hospital (12), it is recommended that discharge from hospital be considered when (Vb, D):

- Sufficient rehydration is achieved as indicated by weight gain and/or clinical status
- Intravenous or enteral fluids are not required
- Oral intake of fluids equals or exceeds losses
- Adequate management by parents is ensured
- Medical follow-up is available via telephone or office visit

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TREATMENT

For the tables of evidence referring to the topics of this section, see Appendix 2, Tables 5.1–5.18.

Rehydration

Oral or Enteral versus Intravenous Rehydration

Oral rehydration should be used as first-line therapy for the management of children with AGE:

- When oral rehydration is not feasible, enteral rehydration by the nasogastric route is as effective if not better than IV rehydration (I, A).
- Enteral rehydration is associated with significantly fewer major adverse events and a shorter hospital stay compared with IV therapy and is successful in most children (I, A).
- Children who are able to receive oral rehydration therapy (ORT) should not be given IV fluids (I, A).

One systematic review (1) of 16 randomized control trials (RCTs) and quasi-RCTs (ie, reviews allocating participants according to date of birth, the number of hospital records, etc) with a search date of June 2003 involving 1545 participants less than 15 years of age with a clinical diagnosis of gastroenteritis found that compared with children treated with IV rehydration, children treated with oral rehydration had significantly fewer major adverse events, including death or seizures (RR 0.36; 95% CI 0.14–0.89), and a significant reduction in length of hospital stay (mean 21 h; 95% CI 8–35). There was no difference in weight gain between the 2 groups

(mean −26 g; 95% CI −61–10). The overall failure rate of enteral therapy was 4% (95% CI 3.0%–5.0%). It was concluded that for childhood gastroenteritis, enteral rehydration is as effective if not better than IV rehydration. Enteral rehydration by the oral or nasogastric route is associated with significantly fewer major adverse events and a shorter hospital stay compared with intravenous therapy (IVT) and is successful in most children.

A more recent systematic review (2) (search date March 2006) identified 17 RCTs and quasi-RCTs involving 1811 participants, of poor to moderate methodological quality, comparing IVT with ORT in children up to 18 years of age with AGE. There were variations in the route of administration of ORT. In 11 trials, ORT was administered by mouth only; in 4 trials, ORS was administered by mouth using a nasogastric tube only when required; and in 1 trial ORS was administered exclusively via nasogastric tube, but previously study enrollment children in both arms had failed a prior uncontrolled trial of ORS administered by mouth. One trial administered ORS exclusively via nasogastric tube, whereas another gave ORS via nasogastric tube in the rehydration phase of the trial and by mouth in the maintenance phase. There were more treatment failures with ORT (risk difference [RD] = 4%; 95% CI = 1–7, random-effects model; 18 trials, 1811 participants, number needed to treat [NNT] = 25). Six deaths occurred in the IVT group and 2 in the ORT group (4 trials). There were no significant differences in weight gain (6 trials, 369 participants), hyponatremia (2 trials, 248 participants) or hypernatremia (10 trials, 1062 participants), duration of diarrhea (8 trials, 960 participants), or total fluid intake at 6 h (985 participants, 8 trials) and 24 h (835 participants, 7 trials). Shorter hospital stays were reported for the ORT group (6 trials, 526 participants, weighted mean difference [WMD] −1.20 days; 95% CI −2.38 to −0.02). Phlebitis occurred more often in the IVT group (number needed to harm [NNH] 50; 95% CI 25–100) and paralytic ileus more often in the ORT group (NNH 33; 95% CI 20–100, fixed-effect model), but there was no significant difference between ORT using the low osmolarity solutions recommended by WHO and IVT (729 participants, 6 trials). It was concluded that although there were no clinically important differences between ORT and IVT, the ORT group did have a higher risk of paralytic ileus, and the IVT group was exposed to risks of IVT. For every 25 children (95% CI 14–100) treated with ORT, 1 would fail and require IVT. A third meta-analysis (3) (search date July 2003) covers data included in the Cochrane Review by Hartling et al (2), and therefore is not discussed here.

Reduced Osmolarity ORS

The classical full-strength WHO-ORS contains Na^+ 90 mmol/L. The so-called ''reduced osmolarity solution,'' which is the current WHO-ORS, contains Na^+ 75 mmol/L. The so-called ''hypotonic osmolarity solution,'' not recommended by WHO but recommended by ESPGHAN (4), contains Na^+ 60 mmol/L.

Reduced or hypotonic osmolarity ORS should be used as first-line therapy for the management of children with AGE.

- *Noncholera diarrhea*: Reduced osmolarity ORS is more effective than full strength ORS, as measured by clinically important outcomes such as reduced stool output, reduced vomiting, and reduced need for supplemental intravenous therapy (I, A).
- The ESPGHAN solution has been used successfully in several RCTs and in a number of non-RCTs in European children. It may be used in children with AGE (II, A).
- *Cholera diarrhea*: Although data were more limited, reduced osmolarity ORS also appears safe and effective for children with cholera (I, A).

Noncholera Diarrhea Two systematic reviews of the same authorship, but different search dates, were found (5,6). The most recent one is discussed here. This Cochrane review (6) sought to compare reduced osmolarity ORS with standard WHO-ORS in children with acute diarrhea. Sixteen RCTs (2297 participants) were found. Studies were from Egypt (n = 2), Bangladesh (n = 3), Mexico (n = 1), Colombia (n = 1), India (n = 3), Panama (n = 1), and the United States (n = 1). Two other studies were multicenter trials; one was conducted in Brazil, India, Mexico, and Peru, and the other in Bangladesh, Brazil, India, Peru, and Vietnam. Participants were children with acute noncholera diarrhea in all trials, except 3 that included cholera patients. In all but one that included children up to 5 years old, the participants' ages ranged between 1 and 36 months. All children had some degree of clinical dehydration. The primary outcome measure, namely unscheduled IV fluid infusion, was reported in 11 trials. In a meta-analysis of 8 trials, reduced osmolarity ORS was associated with fewer unscheduled IV fluid infusions compared with standard WHO-ORS (Mantel Haenzel OR 0.59; 95% CI 0.45–0.79) with no evidence for heterogeneity between trials. No unscheduled IV fluid infusion therapy was required in any participant in 3 trials. Eleven trials reported stool output, and data suggested less stool output in the reduced osmolarity ORS group. Vomiting was less frequent in the reduced osmolarity group in the 6 trials reporting this. Six trials sought hyponatremia, with events in 3 studies, but no obvious difference between the 2 arms. It was concluded that in children admitted to hospital with diarrhea, reduced osmolarity ORS when compared with standard WHO-ORS is associated with fewer unscheduled intravenous fluid infusions, lower stool volume after randomization, and less vomiting. No

additional risk of developing hyponatremia when compared with standard WHO-ORS was detected.

One subsequently published RCT (7) (144 participants)—in male neonates and young children less than 2 months with watery diarrhea less than 72 h and with no or some dehydration—found that reduced osmolarity ORS-75 (mmol/L $Na^+ = 75$, osmolarity = 245) is as safe as standard ORS-90 (mmol/L $Na^+ = 90$; osmolarity = 311) in the treatment of acute watery diarrhea in neonates and very young infants, and is effective in correcting and preventing dehydration.

Cholera Diarrhea One meta-analysis (8) (search date January 2004) of 7 RCTs (797 participants) compared the safety and efficacy of reduced osmolarity ORS with standard ORS for treating diarrhea due to cholera in adults and children. Seven trials (718 participants) met the inclusion criteria for glucose-based reduced osmolarity ORS. Biochemical hyponatremia (serum sodium <130 mmol/L) was more common with reduced osmolarity ORS (RR 1.67; CI 1.09–2.57; 465 participants, 4 trials). It was not significant for severe biochemical hyponatremia (serum sodium <125 mmol/L; RR 1.58; CI 0.62–4.04; 465 participants, 4 trials). No trials reported symptomatic hyponatremia or death. There was no statistically significant difference in the need for unscheduled IV infusion. Analyses separating children and adults showed no obvious trends. Two trials also examined rice-based ORS. In the reduced osmolarity group, duration of diarrhea was shorter (WMD −16.85 h; CI −21.22 to −12.48; 102 participants, 2 trials). It was concluded that in people with cholera, reduced osmolarity ORS is associated with biochemical hyponatremia when compared with standard ORS, although there are similar benefits in terms of other outcomes. Although this risk does not appear to be accompanied by serious consequences, the total patient experience in existing trials is small. Under wider practice conditions, especially when patient monitoring is difficult, caution is warranted.

Based on these and other relevant data, in 2001 the WHO and the United Nations Children's Fund (UNICEF) concluded (9):

1. Reduced osmolarity ORS was more effective than standard ORS for acute noncholera diarrhea in children, as measured by clinically important outcomes such as reduced stool output, reduced vomiting, and reduced need for supplemental IVT. Although data were more limited, reduced-osmolarity ORS also appeared safe and effective for children with cholera.
2. Among adults with cholera, clinical outcomes did not differ among those treated with reduced-osmolarity ORS compared with standard ORS, although there was a risk of transient asymptomatic hyponatremia.
3. Given the programmatic and logistical advantages of using a single ORS composition globally, it was recommended that this be a reduced-osmolarity ORS.
4. Further monitoring, including postmarketing surveillance studies, were strongly encouraged to assess better any risk of symptomatic hyponatremia in cholera-endemic parts of the world. The composition of reduced osmolarity ORS recommended by the WHO is: glucose 75 mmol/L, sodium 75 mEq/L, potassium 20 mEq/L, chloride 65 mEq/L, citrate 10 mmol/L, and osmolarity 245 mOsmol/L.

The above data were extensively discussed by the ESPGHAN-ESPID Working Group, who observed that all of the RCTs included in the 2 Cochrane reviews (6,8) had been conducted in non-European children. In addition, one of the reviews (8) concerned children and adults with cholera. The following points emerged from the working group's discussion:

1. The etiology and clinical consequences of acute diarrhea generally observed in European children are often different from those observed in children from developing countries. In European countries, cholera is not a likely cause of acute diarrhea, malnourished children are less frequently observed, and medical interventions are more widely and readily available. In a Cochrane review published in 2002 (6), an ORS solution containing 60 mmol/L Na^+ (the "ESPGHAN solution") was as effective as standard ORS. One of the studies in the review included as many as 439 children from 4 different countries and was performed by the WHO (10).
2. The so-called "reduced osmolarity solution," namely, the WHO-ORS that contains Na^+ 75 mmol/L, is not available in some European countries.
3. The vast majority of studies performed in European children with AGE in the last decade used the ESPGHAN-ORS. Although these studies were not specifically designed to evaluate oral rehydration, no failures were reported, thereby supporting the safety and efficacy of the ESPGHAN-ORS.

Based on these observations, and given the beneficial effect exerted by the ESPGHAN-ORS on clinically important outcomes, the working group reached the consensus that this ORS is effective in the management of the otherwise healthy child affected by AGE.

Rice-based ORS

Rice-based ORS is not recommended for children with noncholera diarrhea, because it does not result in any additional benefit compared with standard ORS (I, A).

Rice-based ORS can be used as an alternative therapy to standard ORS in children with cholera diarrhea

because it results in a small but important benefit in the management of these children (I, A).

Cereal-based ORS, using such carbohydrate staples as rice-starch or wheat, may reduce diarrhea by adding more substrate to the gut lumen without increasing osmolality, thus providing additional glucose molecules for glucose-mediated absorption. We found 2 meta-analyses by the same authors but with different search dates (11,12). A more recent meta-analysis of 22 clinical trials of rice-based ORS compared with standard ORS found that these solutions appear to be effective in reducing the 24-h stool output in children and adults with cholera, but not in children with noncholera diarrhea. Unlike reduced osmolarity ORS, rice-based ORS did not reduce the need for intravenous infusions (12).

Several more recent RCTs were found (13). However, all trials were performed outside Europe and evaluated the effect of rice-based ORS on cholera and cholera-like diarrhea, which are rarely seen in Europe; thus, the results do not apply directly to the European population.

Super-ORS

Substrates and substances other than rice or cereals have been added to ORS to enhance clinical efficacy. The aims and rationales of this approach are to reduce osmolality while providing increased calories (this has been done with rice as well as glucose polymers); to use substrates that enhance fluid uptake by coupled transport, namely peptides and amino acids; to use substances that release short-chain fatty acids, such as an amylase-resistant starch derived from corn or guar gum, that increase salt and water colonic absorption (the rationale of this novel approach is that the colon possesses a peculiar butyrate/bicarbonate antiport coupled with sodium/proton antiport that may be upregulated to increase fluid salvaging during diarrhea); and to include therapeutic agents against enteric pathogens in ORS, which has been done with the probiotic *Lactobacillus GG* and with diosmectite, a clay that reduces the duration of symptoms of AGE (14).

ORS + Amylase-resistant Starch

Noncholera Diarrhea The evidence is not sufficient to support the use of amylase-resistant starch in all children with AGE (II, B).

Cholera Diarrhea Adolescents and adults with cholera may benefit from the addition to ORS of an amylase-resistant starch, which reduced fecal fluid loss and shortened the duration of diarrhea (II, D, data on adults). Further controlled trials are needed.

A novel way to enhance the clinical efficacy of ORS is to add ingredients that increase the absorptive capacity of the human colon. When undigested carbohydrates, such as an amylase-resistant starch or guar gum, reach the colon they are fermented into short-chain fatty acids that induce colonic absorption of sodium and water from both the normal and the secreting colon (15).

A small randomized trial in 48 adolescents and adults with watery diarrhea due to *Vibrio cholerae* showed that amylase-resistant starch added to standard WHO-ORS reduces stool output. Furthermore, the mean duration of diarrhea was shorter in the amylase-resistant starch group than in either the rice flour or the standard WHO-ORS group (16).

A more recent RCT in randomized children ages 6 months to 3 years with acute diarrhea (human rotavirus 32%, *V cholerae* 6%, other enteropathogens 4%) found that the addition of amylase-resistant starch to standard WHO-ORS, compared with standard ORS, significantly reduced the duration of diarrhea after enrolment by 6.75 h (95% CI 4.3–9.2) (17). Time to first formed stool was also significantly shorter in children receiving experimental ORS (median = 18.3 h; 95% CI 13–23) compared with children receiving standard ORS (median = 21.50 h; 95% CI 17.3–25.7) ($P = 0.04$). The total amount of ORS consumed was similar in the two groups. There was a trend toward a lower mean stool weight in the first 24 hours ($P = 0.075$), as well as a lower total diarrheal stool weight ($P = 0.09$), in patients in the experimental group compared with the control group. It was concluded that in children with acute diarrhea, the addition of amylase-resistant starch to glucose ORS significantly shortened duration of diarrhea compared with standard treatment regardless of the causative agent.

ORS + Guar Gum

ORS with guar gum may be of benefit in children with AGE, but there is insufficient evidence to recommend its routine use (II, B).

In one RCT (18) involving 150 children, partially hydrolyzed guar gum added to standard WHO-ORS compared with the control group substantially reduced the duration of diarrhea (74 ± 37 vs 90 ± 50 h; $P = 0.03$) and modestly reduced stool output in acute noncholera diarrhea in young children. There is insufficient evidence to recommend the use of guar gum in children in Europe. Further controlled trials should be conducted, and a reduced osmolarity ORS should be used rather than the standard WHO-ORS.

ORS + a Mixture of Nondigestible Carbohydrates

A mixture of nondigestible carbohydrates is not recommended for the management of children with AGE (II, B).

A randomized, double-blind, placebo-controlled multicenter study (19) was conducted to evaluate the efficacy and safety of administering a mixture of nondigestible carbohydrates (NDCs) constituted by polysaccharide

25%, α-cellulose 9%, arabic gum 19%, fructooligosaccharides 18.5%, inulin 21.5%, and resistant starch 7%, as an adjunct to ORT in the treatment of acute infectious diarrhea in children with mild to moderate dehydration. In all, 144 boys ages 1 to 36 months with diarrhea defined as 3 or more watery stools per day for greater than 1 day but less than 5 days, and with mild or moderate dehydration (WHO criteria), were randomly assigned to receive hypotonic ORS (Na 60 mmol/L, glucose 111 mmol/L) with or without a mixture of NDCs. Intention-to-treat analysis did not show a significant difference in mean 48-hour stool volumes. The duration of diarrhea after randomization was similar in the 2 groups (82 ± 39 h vs 97 ± 76 h; $P = 0.2$). There was no significant difference in the duration of hospital stay, and unscheduled IV rehydration was comparable in the 2 groups. No adverse effects were noted. The negative results could be due to the type and the amount of NDC added to the ORS. An average dose of 10 to 15 g per episode in relatively mild diarrhea may simply be insufficient to achieve a shorter duration of diarrhea. Furthermore, it is possible that the timing of the intervention was inappropriate because the diarrheal illness was already too severe for the NDCs to be effective.

ORS + Probiotics

ORS with *Lactobacillus GG* may be of benefit in children with AGE, but there is insufficient evidence to recommend its routine use (II, A).

Although there is an abundance of data on the use of probiotics in treating AGE, much less is known about their efficacy if administered in ORS during ORT. One RCT (20) studied the effects of administration of *Lactobacillus GG* (LGG) in ORS. This ESPGHAN multicenter RCT that included 287 children ages 1 month to 3 years with acute-onset diarrhea of all causes found that LGG-supplemented ORS significantly reduced the duration of diarrhea compared with controls (58.3 ± 27.6 vs 71.9 ± 35.8 h; $P = 0.03$), particularly human rotavirus–induced diarrhea (56.2 ± 16.9 h vs 76.6 ± 41.6; $P < 0.008$). The risk of diarrhea lasting longer than 7 days also was reduced significantly in the LGG group (2.7% vs 10.7%; $P < 0.01$), as was hospital stay. It was concluded that administration of ORS containing LGG to children with acute diarrhea is safe and results in a shorter duration of diarrhea, less chance of a protracted course, and faster discharge from the hospital. Further controlled trials should be conducted. The limitation of the ESPGHAN multicenter trial (20) is the lack of an intention-to-treat analysis. See also *Probiotics*.

ORS + Zinc

No RCTs have been carried out in Europe, and such studies are urgently needed. Therefore, despite the clear evidence obtained in malnourished children, there is insufficient evidence to recommend in favor or against the universal addition of zinc to ORS.

Zinc-fortified ORS was evaluated in 1 RCT (21) involving 1219 urban hospitalized Indian children ages 6 to 35 months with acute diarrhea. The total number of stools was lower in the zinc-ORS group (rate ratio 0.83; 95% CI 0.71–0.96), as was the proportion of children with watery stools (OR 0.61; 95% CI 0.39–0.95), compared with the control group; there was no significant effect on diarrhea duration. ORS intake and proportion of children with vomiting did not significantly differ between the zinc-ORS and control groups. The duration of diarrhea was shorter (relative hazards 0.89; 95% CI 0.80–0.99) and the total number of stools was lower (rate ratio 0.73; 95% CI 0.70–0.77) in the zinc syrup group than in control children. Thus, zinc-ORS was moderately efficacious in reducing the severity of acute diarrhea without increasing vomiting or reducing ORS intake. See also *Zinc.*

ORS + Glutamine

ORS with glutamine is not recommended for the treatment of AGE in children (II, A).

Data from one RCT involving 120 male infants, ages between 1 and 12 months, with acute noncholera diarrhea and dehydration showed similar diarrheal stool output, duration of diarrhea, and volume of ORS required to achieve and maintain hydration in children in the glutamine-based ORS vs the control group receiving the standard WHO-ORS (22). See also *Glutamine*.

In summary, although some of the strategies used to develop super-ORS are attractive, they are associated with several problems, namely costs, stability, and availability of additional compounds. At present, super-ORS cannot be considered a priority in efforts to formulate a universal ORS. However, many of these innovative approaches are promising and should not be dismissed.

Nutritional Management

Early versus Late Feeding of a Child With AGE

Children who require rehydration should continue to be fed. Food should not be withdrawn for longer than 4 to 6 hours after the onset of rehydration (I, A).

Clinical practice guidelines of both the American Academy of Pediatrics and ESPGHAN recommend that children with diarrhea who are not dehydrated be fed age-appropriate diets (23,24). Children who require rehydration should be fed starting 4 to 6 hours after the onset of rehydration. Meta-analysis of 4 studies carried out in developed countries showed that early feeding reduced the duration of diarrhea by 0.43 days (95% CI −0.74–0.12) (25–28). Subsequent RCTs

showed that early feeding improved weight gain without increasing treatment failure (either vomiting or diarrhea duration) or the duration of hospital stay (29–32). Even the studies that found no difference in clinical outcomes noted that when continued feeding was recommended the children were more comfortable or their caregivers were more likely to implement the proposed therapy (33,34). It is noteworthy that the results are quite unanimous despite the heterogeneity with regard to patients age (0–36 months; 1 study included children from 0 months, and 2 studies included children ages 2 and 3 months), setting of the study (inpatients and outpatients), and severity of dehydration (mostly mild or moderate dehydration).

A survey of pediatric practice in Europe has shown that food is frequently given later than the recommended 4 to 6 hours after rehydration onset (35). During an open review of a prefinal version of these guidelines at the annual ESPGHAN meeting (Barcelona, Spain, 2007), it was observed that 4 to 6 hours cannot be considered an ''interruption'' of feeding, thereby challenging the traditional concept of ''refeeding.''

Should Breast-feeding Be Stopped Dduring Gastroenteritis?

Continue breast-feeding during acute gastroenteritis (III, C).

Continuing breast-feeding during AGE has been shown to exert a beneficial effect by reducing the number and volume of diarrheal stools and reducing the duration of diarrhea in rotavirus gastroenteritis, although only 2 studies have specifically evaluated this intervention (36,37). Both the American Academy of Pediatrics (23) and ESPGHAN (24) recommend that breast-feeding be continued anytime during an episode of diarrhea.

Is Formula Dilution or the Gradual Reintroduction of Feeding Effective?

Formula dilution and gradual reintroduction of feeding is not needed (I, A).

For the optimal management of mild to moderate dehydrated children in Europe, normal feeding should be continued no later than 4 to 6 hours after the onset of rehydration (I, A).

A meta-analysis conducted in 1994 (38) identified 16 studies (9 RCTs) that investigated the practice of diluting formula 2- to 6-fold for periods ranging from 1 to 6 days, or in some cases until the severity of diarrhea declined.

Treatment Failure Rates Fourteen studies reported data on treatment failure rates. The pooled treatment failure rate was 16% (95% CI 11%–18%) for undiluted milk and 12% (95% CI 7%–13%; $P = 0.05$) for diluted milk. When only studies of patients with more severe dehydration were compared, the treatment failure rates with undiluted milk (20%; 95% CI 15%–25%) were greater than the rates with diluted diets (95% CI 10%–17%; $P = 0.003$). The RR of treatment failure was 2.0 (95% CI 1.2–3.3). When studies of patients with milder disease were analyzed, the treatment failure rates were 14% (95% CI 10%–17%) and 13% (95% CI 10%–17%) with undiluted and diluted milk, respectively. An RR of 1.1 (95% CI 0.7–1.6) was not significant. Thus, any adverse effect of continuing undiluted milk was limited to patients with more severe illness.

In a separate analysis of studies performed before and after 1985, the pooled treatment failure of earlier studies was 21% (95% CI 16%–26%) with undiluted milk and 10% (95% CI 6%–14%) with diluted milk ($P = 0.005$). There were no differences in pooled treatment failure rates among the respective groups in the later studies (14% vs 12%). The difference is probably attributable to the practice of starving children for 24 to 48 hours, which was discontinued after 1985.

Stool Frequency and Stool Amount The pooled data (6 studies) suggest that there was a slight increase in stool frequency with continued use of undiluted milk ($P = 0.046$). The analyses of both stool frequency and volume indicate that early introduction (ie, 4–6 h after the onset of rehydration) of an undiluted lactose-containing milk diet is associated with a slight increase in stool output compared with diluted milk. However, these differences are probably of minor clinical importance.

Duration of Diarrhea The pooled data from 10 studies indicate that the duration of diarrhea did not differ between the dietary groups studied.

Weight Gain The pooled data from 7 studies demonstrate that undiluted milk feeding resulted in a significant body weight catch-up ($P = 0.002$).

A variety of early feeding regimens has been studied, including human milk, adapted cow's milk formulas, soy-based lactose-free formulas, and staple food or cereals with milk (25,29–32,34,39). These studies demonstrated that unrestricted diets do not worsen the course or symptoms of mild diarrhea compared with ORS or intravenous therapy alone.

Regarding the frequency of feeding, in the only study conducted after 1997 to evaluate feeding rates, it was shown that decreasing the volume of each feed and increasing the frequency of feedings while maintaining the total amount of food speeds recovery and increases weight gain in Chinese children (40).

In conclusion, the studies published after 1985 (27–29,41–45) showed no increased risk of treatment failure with undiluted milk compared with diluted milk regardless of the type of feeding investigated. Notably, the small clinical advantage of decreased stool frequency and

amount obtained by feeding diluted milk was offset by the poorer weight gains of children on these regimens. No studies were published after 1997 (24).

Are Lactose-free or Other Elimination Diets/Formulas Indicated for AGE?

The vast majority of young children with AGE can safely continue to receive lactose-containing milk formula because the number of treatment failures is negligible vs children with acute diarrhea on a lactose-free diet (I, A).

The meta-analysis by Brown et al published in 1994 (38) identified 14 studies, and several outcomes were analyzed.

Treatment Failure Rates Overall, 22% (95% CI 18%–27%) of children who consumed lactose were therapeutic failures compared with 12% (95% CI 9%–15%) of those who did not ($P < 0.0001$); pooled RR 2.1 (95% CI 1.6–2.7). However, the results were widely heterogeneous (Breslow-Day test, OR) ($P = 0.016$). Among studies that considered the initial severity of diarrhea and dehydration, there was an increased rate of treatment failure among patients on lactose-containing diets, 38% (95% CI 31%–44%) compared with 16% (95% CI 12%–20%) in nonlactose groups ($P < 0.0001$; RR 2.4; 95% CI 1.8–3.3). However, the excess treatment failure rates occurred only in studies that included patients whose initial degree of dehydration was severe. In studies of only patients with less severe dehydration, the treatment failure rates in the lactose groups were 7% (95% CI 5%–12%), ie similar to those in the nonlactose groups (8%, 95% CI 5%–12%; RR 1.0, CI 0.5–1.9). All but one of the studies that detected higher rates of treatment failure with lactose-containing diets were performed before 1980, when standardized treatment was not widely implemented. Studies that reported higher treatment failures also were more likely to use stool frequency or duration of diarrhea to define treatment failure, whereas the other studies relied more on failure criteria such as recurrent dehydration or weight loss, which are of greater clinical relevance.

Stool Frequency and Stool Amount Only 4 of 14 studies provided information about stool frequency and outputs. Lactose-containing formulas caused marginally greater stool outputs than the lactose-free formulas, although these differences are unlikely to be of clinical importance except possibly among the children with previous treatment failure or severe underlying malnutrition.

Duration of Diarrhea Nine studies reported data on the duration of diarrhea after initiation of therapy. The pooled results showed a small but significant increase in the mean duration of diarrhea that ranged from −85 to 67 hours when lactose-containing milk was consumed ($P = 0.001$). However, the results were widely heterogeneous ($P = 0.003$). It seems that inclusion of lactose-containing products in diets composed exclusively of milk or infant formula increased the duration of diarrhea. When other solid foods were provided in addition to milk, the inclusion of lactose in the mixed diet did not appear to affect the duration of illness.

Weight Gain Few studies reported data on change in body weight during therapy. Thus, the effect on weight change could not be reliably assessed.

The above results confirm that most young children with AGE can safely continue to receive undiluted milk formula.

The only study published after the Brown et al (38) metanalysis of the use of nonhuman milks in the dietary management of young children with acute diarrhea compared soy-based formula with lactose or sucrose in well-nourished children ages 3 to 18 months from Egypt, and showed significantly lower stool output, shorter diarrhea duration, and fewer treatment failures with sucrose-containing formula (46).

Are Soy Formula and Elimination Diets Effective?

We did not find any data supporting the need to routinely switch from a cow's milk–based formula to a soy or hydrolyzate formula in a baby with AGE. This is true also in the first 2 months of life (III, C).

It was formerly suggested that cow's milk protein be withdrawn in a weaned baby with AGE to prevent the development of sensitization. In 2 studies that evaluated several types of feeding during AGE (soy-based, cow's milk–based, and whey hydrolyzed formulas), there was no advantage for soy formula with regard to severity and duration of diarrhea, duration of hospitalization, or treatment failure (42,47). Similarly, no data support the routine use of casein or whey hydrolyzate in AGE (43,48). It must be noted that all studies were performed before 1991, included a heterogeneous population of children (inpatients and outpatients, different degrees of dehydration, different nutritional status, and different protocol interventions and outcomes) with less than 75 patients in each intervention group.

The American Academy of Pediatrics and ESPGHAN recommendations (23,24) on the use of these formulas state that there is no evidence to justify the use of hydrolyzed formulas in children older than 3 months. No studies have been carried out in children below 3 months of age. The guidelines' working group discussed the use of elimination diets in the first 2 months of life, and because no evidence was found, it was agreed to recommend continuing cow's milk protein–containing

formula. In addition, cow's milk–based formula also should be continued in weaned babies with mild to moderate diarrhea.

The bread, rice, apple, toast (BRAT) diet has not been studied and is not recommended (Vb, D). Beverages with a high sugar content should not be used (III, C).

The clinical and nutritional outcomes of a variety of foods and diets have been evaluated in children with AGE.

Soy fiber. Formulas containing soy fiber have been marketed in the United States, and have been reported to reduce liquid stools without changing overall stool output (49,50). However, this outcome is not sufficient to recommend the use of these formulas as standard care.

Yogurt. Yogurt has been used as a component of rehabilitation diets either alone or in mixtures (38,51,52), and has been shown to lead to significant improvement in clinical symptoms (stool volume and frequency). It is not a standard food and therefore its effects may not be consistent.

Cereal-milk mixtures. Several studies have incorporated regimes of cereal-milk mixtures (53) and found them safe and even better than simple formulas (lower treatment failures, fecal output, duration of diarrhea, and better weight gain).

Home-available staple foods/milk-free diets. Several studies performed in developing countries have shown that mixtures of accessible staple foods (cereals, vegetables, bread, yogurt, and chicken) are safe to use during diarrheal illness (34,54–57), are nutritionally adequate, and have the advantage of low cost and availability, as compared with industrial formulas. However, these issues are not relevant for affluent Western societies, and the use of these feeding regimens has not been extensively evaluated in developed countries.

Solid foods. Weaned children should be fed whatever they eat normally. Full feeding appropriate-for-age foods are well tolerated and are definitely better than the practice of withholding food (better weight gain, without increasing complication rates or treatment failures) (32) (III, C).

Amylase-digested starch. The use of amylase-digested porridge with high-density energy, which is a highly palatable and low viscosity feed, has been evaluated in 2 studies in children with AGE from developing countries. These inexpensive technologies are appropriate for developing countries, but have not been studied in other settings.

The BRAT diet of bread, rice, apples, and toast is a limited diet low in energy density, protein, and fat that was formerly empirically recommended, although no studies have ever evaluated its safety or efficacy.

Tea, juices, soft drinks. Beverages with a high sugar content should be avoided. Two studies from Brazil (58,59) compared the use of fruit juices with different fructose/glucose ratios during early and late refeeding as an addition to age-appropriate milk formulas and complementary foods. They showed that although intake of these juices resulted in more fecal losses and prolonged diarrhea, patients drinking them ingested more calories and gained more weight. However, this intervention was not compared with the standard recommendation of ORS supplementation as needed during refeeding. Owing to the risk of inducing further fluid losses as a consequence of increased osmotic load, drinks with a high carbohydrate concentration should be avoided.

In conclusion, controlled clinical trials suggest that complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables are well tolerated in children with mild to moderate diarrhea and should be continued unrestricted as age-appropriate foods after the period of rehydration.

Pharmacological Therapy

Antiemetics

Despite some clinical benefits, we suggest that antiemetics should not be routinely used to treat vomiting during AGE in children (II, B).

Vomiting is a common symptom in children with gastroenteritis, but its treatment remains controversial. In position papers, authoritative scientific societies and expert groups recommend antiemetics be avoided in young children with vomiting associated with acute diarrhea because of potential troublesome side effects and questionable benefit (24,60,61). However, both physicians and caregivers are interested in interventions that will increase the likelihood of ORT being successful.

A recent Cochrane review (62) of 3 RCTs (396 participants) investigated the efficacy of antiemetics on gastroenteritis-induced vomiting in children and adolescents. It was found that there is some evidence, albeit weak and not reliable, that antiemetics such as ondansetron (a 5-HT_3 serotonin antagonist) and metoclopramide (a dopamine antagonist), compared with placebo, reduce the number of episodes of vomiting due to gastroenteritis in children. The increased incidence of diarrhea noted with both ondansetron and metoclopramide was considered to be a result of retention of fluids and toxins that would otherwise have been eliminated through the process of vomiting.

A meta-analysis (63) of 4 RCTs involving 490 patients investigated the potential beneficial effects of ondansetron, compared with placebo or no intervention, in controlling vomiting during AGE in children. Combined data

from 3 RCTs (466 participants) showed that ondansetron compared with the control significantly increased the chance of vomiting cessation soon after drug administration (RR 1.3, 95% CI 1.2–1.5; NNT 5, 95% CI 4–8), but this effect was not observed at 24 hours (2 RCTs, 144 participants; RR 1.2, 95% CI 0.9–1.7). Ondansetron significantly reduced the risk of intravenous rehydration (2 RCTs, 359 participants; RR 0.4, 95% CI 0.3–0.7; NNT 7, 95% CI 5–14). Outcome measures not significantly different after ondansetron treatment were the need for hospitalization and return emergency department visits.

In summary, despite some clinical benefits, there is no evidence to recommend the routine use of ondansetron for vomiting during AGE in children because of safety concerns (increased number of diarrheal stools). Costs may be an issue. The use of metoclopramide can be associated with some troublesome side effects, namely sedation and extrapyramidal reactions that occur frequently with standard doses (64–66). Given these considerations, the routine use of antiemetic drugs in young children with vomiting associated with AGE is questionable. However, antiemetics may be of value for selected children with severe vomiting, but this should be evaluated in RCTs performed in this specific population.

Antimotility or Antiperistaltic Drugs

Loperamide Loperamide should not be used in the management of AGE in children (II, B).

Loperamide is an opioid receptor agonist that reduces intestinal lumen motility (67). It is used for short-term symptomatic relief of acute diarrhea in adults (68). We found 1 systematic review with a meta-analysis of RCTs designed to assess the efficacy of loperamide for the treatment of acute diarrhea in children younger than 12 years (69). Thirteen RTCs (1788 participants) met the inclusion criteria. Most of the trials had important limitations. Generation of the allocation sequence was reported in only 1 trial. Allocation concealment was adequate in 7 trials. Only 9 trials were double-blind; the remaining 4 were open trials. Intention-to-treat analysis was performed in only some trials. Only 6 studies met all indicators of methodological quality used by the reviewers. Many studies were carried out in non-European countries. Combined data from 4 RCTs showed that loperamide compared with placebo reduced the risk of diarrhea at 24 hours (RR 0.66, 95% CI 0.57–0.78) and at 48 hours (RR 0.59, 95% CI 0.45–0.78). Loperamide also reduced the duration of diarrhea (6 trials; WMD −0.8 days, 95% CI −0.87 to −0.74), and the number of stools at 24 hours (4 trials; count ratio 0.84, 95% CI 0.77–0.92). All findings were stable when random-effects models were used. Serious adverse events, defined as lethargy or death, were reported in 8 out of 972 children allocated to loperamide (0.9%, 95% CI 0.4%–1.7%) compared with none of 764 children allocated to placebo (0%, 95% CI 0%–0.5%). All serious adverse events were reported in children less than 3 years of age. The authors concluded that in children who are less than 3 years of age, malnourished, moderately or severely dehydrated, systematically ill, or with bloody diarrhea, the risk of adverse events outweighs the benefits, even at doses less than 0.25 mg/kg/day. In contrast, in children older than 3 years of age with no or minimal dehydration, loperamide may be a useful adjunct to ORT. In summary, loperamide reduced the duration of diarrhea in some trials, but because it may exert life-threatening effects, it should not be used for the management of AGE in infants and young children.

Adsorbents

Smectite Smectite may be considered in the management of AGE (II, B).

Smectite is a natural hydrated aluminomagnesium silicate that binds to digestive mucus (70) and has the ability to bind endo- and exotoxins, bacteria, and rotavirus (71,72). In experimental models, smectite increased water and electrolyte absorption and restored the barrier properties of human intestinal cell monolayers after exposure to tumor necrosis factor (TNF)-α (73). It also modified the activity of bile salts and the physical properties of gastric mucus, thereby counteracting mucolysis induced by bacteria (2). Although it is currently not recommended by such medical institutions as ESPGHAN (74), WHO (75), or the American Academy of Pediatrics (23,60), smectite is frequently used to treat acute infectious diarrhea in several countries, particularly in France and most countries of Central and Eastern Europe (35). A recent review (76) systematically evaluated the efficacy of smectite in treating acute infectious diarrhea in infants and children. Nine RCTs (1238 participants) met the inclusion criteria. Most of the trials had important limitations. Allocation concealment was adequate in only 1 trial. Only 3 were double-blind. The remaining were open trials. Intention-to-treat analysis was performed in only 5 trials. Combined data from 6 RCTs showed that smectite significantly reduced the duration of diarrhea compared with placebo. The pooled WMD was −22.7 hours (95% CI −24.8 to −20.6) with a fixed model and remained significant in a random effect model (−24.4 h, 95% CI −29.8 to −19.1). The chance of cure on intervention day 3 was significantly increased in the smectite vs the control group (RR 1.64, 95% CI 1.36–1.98; NNT 4, 95% CI 3–5). Adverse effects were similar in the 2 groups.

The results emerging from this meta-analysis are promising, and smectite may be used in AGE as an adjunct to standard rehydration therapy. However, these results should be interpreted with caution, because most of the included studies had important limitations. Also, cost-effective analyses should be undertaken before routine pharmacological therapy with smectite is universally

recommended. Furthermore, it is important to delineate the groups (out-patient vs in-patient, older vs younger, viral vs other etiology of diarrhea) that derive the greatest clinical benefit from smectite therapy.

Kaolin-pectin Kaolin-pectin is not recommended for the treatment of AGE in children (III, C).

Four RCTs (77–80) examined the effect of kaolin-pectin on acute diarrhea symptoms. Trials were often of poor quality (ie, no blinding to treatment allocation or no placebo control). There is insufficient evidence to make a recommendation on the use of kaolin-pectin for the management of AGE in children.

Attapulgite There is insufficient evidence to recommend the use of attapulgite.

Attapulgite is a hydrated magnesium aluminum silicate that supposedly adsorbs large numbers of bacteria and toxins and reduces water loss. One review (81) summarized data on clinical trials on attapulgite for the treatment of acute diarrhea in infants and children in France and Africa. A total of 7616 infants and children were entered into these open or placebo-controlled trials. Most patients were under 2 years of age. The authors concluded that the results of the analysis confirmed the antidiarrheal efficacy and safety of attapulgite. Many studies were of poor quality with lack of blinding to treatment allocation, no placebo control, or very small numbers. There is insufficient evidence to make a recommendation on the routine use of attapulgite for the treatment of AGE in children.

Activated Charcoal Activated charcoal is not recommended for the treatment of AGE in children.

We did not identify any RCT regarding the use of activated charcoal in the treatment of AGE in children.

Antisecretory Drugs

Bismuth Subsalicylate We suggest that bismuth subsalicylate not be routinely used in the management of children with AGE (III, B).

Bismuth subsalicylate or other bismuth salts preparations are common constituents of over-the-counter medications for diarrhea. Although the precise mechanism of their action remains unknown, their effect was thought to be due to antisecretory and antimicrobial properties (82–84).

Three randomized controlled trials that compared bismuth subsalicylate with placebo in infants with acute watery diarrhea found that bismuth subsalicylate only modestly reduced the duration and severity of diarrhea (85–87). All trials were carried out in non-European populations (Bangladesh, Peru, and Chile). In addition to harmless, temporary side effects (ie, darkening of the tongue and stool), bismuth subsalicylate has been reported to cause salicylate toxicity in children (88).

Racecadotril Racecadotril may be considered in the management of AGE (II, B). However, well-designed prospective studies of efficacy and safety should be carried out in outpatient children.

Racecadotril (acetorphan) is an antisecretory drug that exerts its antidiarrheal effects by inhibiting intestinal enkephalinase, thereby preventing the breakdown of endogenous opioids (enkephalins) in the gastrointestinal tract and reducing secretion of water and electrolytes into the gut (89).

One RCT (90) involved 135 boys ages 3 to 35 months (mean 13 months) with watery diarrhea for 5 days or more who had passed 3 diarrheic stools or more within 24 hours of admission to hospital, and had passed 1 diarrheic stool or more within 4 to 6 hours of admission. Intention-to-treat analysis showed that children receiving racecadotril (1.5 mg/kg of body weight) orally every 8 hours ($n = 68$) as an adjunct to ORT, compared with oral rehydration alone ($n = 67$), had a lower mean 48-hour stool output than patients who received placebo ($P < 0.001$). The mean total stool output was lower in the racecadotril group than in the placebo group ($P < 0.001$). More patients who received racecadotril were cured by 5 days vs patients who received placebo (RR 1.3, 95% CI 1.04–1.6; NNT 6, 95% CI 4–29; $P = 0.015$). The total intake of ORS was lower in the racecadotril group ($P < 0.001$). The groups did not differ in adverse effects (10% vs 7%), none of which was severe. It was concluded that in children with severe watery diarrhea, racecadotril as an adjunct to ORT reduced stool output, duration of diarrhea, and intake of ORS.

In another RCT (91) involving 172 infants ages 3 months to 4 years (mean age 12.8 months) with acute diarrhea, it was found that during the first 48 hours of treatment, patients receiving racecadotril (1.5 mg/kg administered orally 3 times daily) had a significantly lower stool output (grams per hour) than those receiving placebo. The 95% CI was 43% to 88% for the full data set ($n = 166$; $P = 0.009$) and 33% to 75% for the per-protocol population ($n = 116$; $P = 0.001$). There was no difference between treatments depending on rotavirus status. Significant differences between treatment groups also were found after 24 hours of treatment: full data set ($n = 167$; $P = 0.026$) and per-protocol population ($n = 121$; $P = 0.015$). Tolerability was good in both groups of patients. This study demonstrates the efficacy (up to 50% reduction in stool output) and tolerability of racecadotril as adjuvant therapy to ORS in the treatment of severe diarrhea in infants and children.

A third RCT (92) in 166 hospitalized children ages from 3 months to 3 years with acute diarrhea found a reduced number of emergency department visits after starting racecadotril treatment ($P < 0.05$) and a reduced

number of stools during the first 48 hours ($P < 0.001$). There was no difference in weight gain on day 7. In summary, in 3 relatively small RCTs with some methodological problems, 2 conducted in hospitalized children, in developed and developing countries, racecadotril was effective in reducing the volume and frequency of stool output and in reducing the duration of diarrhea (particularly in children with rotavirus diarrhea). There is evidence in favor of the use of racecadotril over placebo or no intervention to reduce the stool output in children with AGE. However, this evidence is based mainly on inpatient data, and does not take into account safety concerns that can be resolved either in studies involving large cohorts of children or in postmarketing surveillance evaluation, which is mandatory before therapy with racecadotril can be recommended.

The use of racecadotril was discussed at length during the open review of a prefinal version of these guidelines at the 2007 annual meeting of ESPGHAN (Barcelona, Spain), and the recommendation was reformulated based on the input received on that occasion.

Probiotics

Probiotics may be an effective adjunct to the management of diarrhea. However, because there is no evidence of efficacy for many preparations, we suggest the use of probiotic strains with *proven efficacy* and in appropriate doses for the management of children with AGE as an adjunct to rehydration therapy (II, B).

The following probiotics showed benefit in meta-analyses of RCTs: *Lactobacillus GG* (I, A) and *Saccharomyces boulardii* (II, B).

Evidence of lack of risk of antibiotic resistance transfer is required for probiotics proposed for clinical use (Vb, D).

Probiotics are living microorganisms that, upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition (93). The most commonly used strains are lactic acid bacteria, such as lactobacilli or bifidobacteria, and the nonpathogenic yeast *S boulardii*. The rationale for the use of probiotics to treat and prevent diarrheal diseases is based on the assumption that they modify the composition of the colonic microflora and act against enteric pathogens. However, the exact mechanism by which probiotics exert their activity against enteropathogens in humans remains unknown. Several possible mechanisms have been proposed, mostly based on the results of in vitro and animal studies (94–113).

Meta-analyses Assessing Probiotic Efficacy Four meta-analyses aimed at evaluating the effect of probiotics in the treatment of acute infectious diarrhea have been published. In the first (114), MEDLINE and the Cochrane Controlled Trials Register were searched (search date April 2001). Ten RCTs comparing probiotics versus placebo in children ages 1 to 48 months with acute infectious diarrhea were identified. A qualitative assessment of the validity of the studies was done using the Jadad criteria (115). All studies involved hospitalized patients, except 1 that included a small group of outpatients; most were conducted in developed countries. Probiotics (LGG, *Lactobacillus reuteri* (ATCC 55730), *L acidophilus* LB, *S boulardii*, and a mixture of *Streptococcus thermophilus, L acidophilus*, and *L bulgaricus*) significantly reduced the duration of diarrhea when compared with placebo, particularly in rotaviral gastroenteritis. The pooled WMD assuming the random-effect model was −20.1 hours (95% CI −26 to −14) and −25 (95% CI −32 to −18), respectively.

In the second meta-analysis (116) (search date 2000) 9 RCTs (n = 765) that compared treatment with the use of different *Lactobacillus* species (LGG, *L reuteri* ATCC 55730, and *L acidophilus/bulgaricus*) with placebo were included in the review (8 of which were also identified in the above-mentioned meta-analysis). In the *Lactobacillus* group vs placebo group, the summary point estimate showed a significant reduction in diarrhea duration of 17 hours (95% CI 7–29) and a reduction in diarrheal stool frequency of 1.6 stools on day 2 of treatment (95% CI 0.7–2.6). A preplanned subgroup analysis suggested a positive dose-dependent relationship between the logarithm of the daily *Lactobacillus* dose and the reduction of diarrhea duration in days (with a dose $>10^{11}$ colony-forming units/48 h being the most effective).

The authors of the third meta-analysis (117) searched MEDLINE, EMBASE, and the Cumulative Index to Nursing and Allied Health database from 1966 to December 2001. Abstracts from relevant major meetings and reference lists also were searched. A total of 18 RCTs (1917 participants) were included. The probiotic strains used in these studies were LGG, *L acidophilus, L bulgaricus, S thermophilus, L rhamnosus, Yalacta (L rhamnosus, L delbrueckii, L bulgaricus), L reuteri, Enterococcus* SF68, *S boulardii, Bacillus subtilis, B bifidum*, and *B infantis*. The results of this meta-analysis provide evidence of the efficacy of probiotic supplements in reducing the duration of symptoms among children up to 5 years of age with acute, nonbacterial diarrhea. Probiotics, and particularly lactobacilli, reduced the duration of an acute diarrheal episode in an infant or child by approximately 1 day. It is noteworthy that there was significant heterogeneity between the studies.

In the fourth meta-analysis (118) (searched up to 2002), 23 studies with a total of 1917 participants met the inclusion criteria. There were 1449 infants or children (age <18 years) and 352 adults (age ≥18 years). Several different probiotics were tested; all were lactic acid bacilli, except in 2 studies in which the yeast *S boulardii* was tested. Treatment regimens varied widely as to the number of organisms administered, timing of the intervention, means of administration, and duration of

treatment. The trials also varied in methodological quality as well as in definitions and outcomes of diarrhea. Despite the wide variability between studies, nearly all trials demonstrated a beneficial effect of probiotics in reducing diarrhea, and this effect was statistically significant in many studies. The pooled results showed that probiotics reduced the risk of diarrhea at 3 days (RR 0.7, 95% CI 0.6–0.8, random effects model; 15 studies) and the mean duration of diarrhea by 30.5 hours (95% CI 19–43, random effects model; 12 studies). The authors concluded that probiotics appear to be a useful adjunct to rehydration therapy in treating acute, infectious diarrhea in adults and children.

Critics of using a meta-analytical approach to assess the efficacy of probiotics argue that beneficial effects of probiotics seem to be strain-specific; thus, pooling data on different strains may result in misleading conclusions. Consequently, 2 recent meta-analyses focused on a single probiotic rather than on probiotics in general. The first meta-analysis (119) (search date August 2006) of 5 randomized-controlled trials (619 participants) showed that *S boulardii* significantly reduced the duration of diarrhea compared with control. The pooled WMD was −1.1 days (95% CI −1.3 to −0.8) with a fixed model and remained significant in a random-effect model. *S boulardii* significantly reduced the risk of diarrhea on days 3, 6, and 7. Also the risk of diarrhea lasting greater than 7 days was significantly reduced in the *S boulardii* group vs the control group (1 RCT, 88 participants; RR 0.25, 95% CI 0.08–0.83; NNT 5, 95% CI 3–20). It was concluded that *S boulardii* therapy results in a moderate clinical benefit, mainly a shorter duration of diarrhea, in otherwise healthy infants and children with AGE. However, these results should be interpreted with caution due to methodological limitations of the studies included in the meta-analysis.

The second meta-analysis (120) of 8 RCTs (search date August 2006) involving 988 children with acute infectious diarrhea found that, compared with controls, LGG had no effect on the total stool volume (2 RCTs, 303 participants). However, LGG was associated with a significant reduction in diarrhea duration (7 RCTs, 876 infants; WMD −1.1 days, 95% CI −1.9 to− 0.3), particularly of rotavirus diarrhea etiology (WMD −2.1 days, 95% CI −3.6 to −0.6), risk of diarrhea greater than 7 days (1 RCT, n = 287; RR 0.25, 95% CI 0.09–0.75), and duration of hospitalization (3 RCTs, n = 535; WMD −0.58, 95% CI −0.8 to −0.4; significance was lost in the random-effect model). There was no reduction in the number of stools at any time interval. It was concluded that the use of LGG is associated with moderate clinical benefits in the treatment of acute diarrhea in children. These findings should be interpreted with caution owing to the important methodological limitations and heterogeneity of most of the studies.

A recent randomized controlled trial with 5 probiotic preparations administered in parallel to outpatient children with AGE showed that 2 of these preparations (LGG and a mix of 4 different probiotics) shortened the duration of diarrhea compared with ORS alone, whereas the other 3 (*S boulardii, B clausii,* and*E faecium* SF68 had no effect (121).

In summary, data from several meta-analyses consistently show a statistically significant effect and moderate clinical benefit of selected probiotic strains in the treatment of acute watery diarrhea (primarily rotaviral), mainly in infants and young children. The beneficial effects of probiotics in acute diarrhea in children seem to be: moderate, strain-dependent, dose-dependent (greater for doses $>10^{10}$–10^{11} colony-forming units), significant for watery diarrhea and viral gastroenteritis but not for invasive bacterial diarrhea, more evident when treatment with probiotics is initiated early in the course of disease, and more evident in children in developed countries.

LGG and *S boulardii* were found to be beneficial in meta-analyses devoted to single probiotics. Other probiotics also may be used provided their efficacy is documented in high quality RCTs (or in meta-analyses). Safety issues with probiotics are related to bacterial translocation and sepsis and to the risk of antibiotic resistance. While bacterial translocation seems an exceptional event, antibiotic resistance may be a true problem in terms of safety. Evidence of antibiotic resistance has been reported for some probiotic or candidate probiotic strains, among which are *L reuteri* ATCC 55730 and *E faecium* (122–125). International authorities (Food and Agriculture Organization/WHO 2001 and 2002, and the European Food Safety Authority document on qualified presumption of safety) require proof of absence of drug resistance and the demonstration of nontransferability of this trait for all probiotic bacteria. The ESPGHAN/ESPID Working Group fully endorses this recommendation.

Prebiotics

We do not suggest the use of prebiotics in the management of children with AGE (II, B). However, only a few prebiotics have been studied.

Prebiotics are defined as nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of 1 or of a limited number of bacteria in the colon, thereby improving host health (126).

In addition to the information given under the section entitled *ORS + Mixture of Nondigestible Carbohydrates*, in a large, well-designed study performed in Peruvian infants ages 6 to 12 months (n = 282), Duggan et al (127) compared an infant oligofructose-supplemented cereal (0.55 g/15 g cereal) with a nonsupplemented cereal. There was no difference in the number of diarrheal episodes (4 ± 2.9 vs 4.0 ± 3.5), episodes of severe diarrhea (1.3 ± 1.5 vs 1.1 ± 1.2), or episodes of dysentery (0.2 ± 0.6 vs 0.1 ± 0.4). No significant difference was found in the

mean duration of diarrhea (10.3 ± 9.6 vs 9.8 ± 11.0 days). During a second part of the same trial involving 349 subjects, zinc (1 mg/15 g cereal) was added to both oligofructose-supplemented and control cereals (127). Again, no significant difference was found in the number of episodes of diarrhea (3.7 ± 2.6 vs 3.7 ± 2.3), episodes of severe diarrhea (1.5 ± 1.4 vs 1.3 ± 1.3), episodes of dysentery (0.2 ± 0.4 vs 0.1 ± 0.4), or mean duration of diarrhea (10.3 ± 8.9 vs 9.5 ± 8.9 days). It must be emphasized that these studies were designed as preventive, not therapeutic, and may therefore be underpowered to detect a significant reduction of diarrheal symptoms.

Currently, prebiotics are not recommended for the treatment of AGE. However, few prebiotics have been tested. Other rigorous, systematic trials on prebiotics are warranted.

Homeopathy

Although homeopathy continues to be widely used, there is insufficient evidence to recommend its use for the treatment of AGE in children (III, C).

The role of homeopathic remedies in the treatment of acute childhood diarrhea is still controversial. A recent meta-analysis of 3 RCTs involving 242 children ages 6 months to 5 years carried out in non-European populations (Nicaragua and Nepal) suggests that some homeopathic remedies decrease the duration of acute diarrhea in children (128). One RCT involving 292 children with acute diarrhea tested a combination of the 5 most common single homeopathic remedies. The homeopathic combination therapy tested in this study did not significantly reduce the duration or severity of acute diarrhea in Honduran children (129). Even if future studies confirm the efficacy of homeopathic drugs, the exact mechanism by which they could have exerted their activity is unclear. The results of the studies cannot be extrapolated to the European population. Specific recommendations regarding the use of homeopathy should await further well-conducted human trials.

Herbal Medicine

There is insufficient evidence to recommend in favor or against the use of herbal medicine for the treatment of AGE in children (III, C).

No systematic review on herbal medicine for the treatment of acute diarrhea in children was found. One RCT (130) was performed in 40 Russian children ages between 3 months and 7 years with rotavirus diarrhea. The study group received a tormentil root extract. The duration of diarrhea was significantly reduced in the treatment group ($P = 0.0001$). Sample size was small and the extract preparation does not appear to be well-standardized. In addition, there may be gastrointestinal side effects. Based on the amount of information available, herbal medicine is not recommended.

Micronutrients

Zinc UNICEF and WHO recommend zinc supplementation (10 mg below 6 months of age and 20 mg in older infants and children for 10–14 days) as a universal treatment for children with diarrhea.

Although there is no major safety issue regarding zinc supplementation, there is also no proven benefit of its use in European children with AGE (III, C). Given the WHO recommendation, zinc should be given to any malnourished child.

Zinc deficiency, which is common in young children in the developing world, is associated with impaired water and electrolyte absorption (131–134), decreased brush border enzymes (135–137), and impaired cellular and humoral immunity (138–141). Because intestinal losses of zinc are considerably increased during acute diarrhea (142,143), a number of trials evaluated the effect of zinc supplements on diarrheal diseases. The findings suggest that in developing countries, zinc supplementation results in clinically important reductions in the duration and severity of acute diarrhea when given as an adjunct to oral rehydration therapy (144–149). In an RCT open-label study in well nourished Turkish children, zinc therapy (15–30 mg/day) increased zinc levels, but it did not change either the duration or severity of diarrhea (150).

The CDC (151) stated that a number of trials have supported zinc supplementation as an effective agent in treating and preventing diarrheal disease; however, further research is needed to identify the mechanism of action of zinc and to determine its optimal delivery to the neediest populations. The role of zinc supplements in developed countries needs further evaluation.

The position of WHO is that zinc deficiency is widespread among children in developing countries and occurs in most parts of Latin America, Africa, the Middle East, and South Asia (152). However, convincing evidence of its importance in child health has come only recently from RCTs of zinc supplementation. Numerous studies have shown that zinc supplementation (10–20 mg/day until cessation of diarrhea) significantly reduces the severity and duration of diarrhea in children less than 5 years of age. Additional studies have shown that short-course supplementation with zinc (10–20 mg/day for 10–14 days) reduces the incidence of diarrhea for 2 to 3 months. Based on these studies, WHO now recommends that zinc (10–20 mg/day) be given for 10 to 14 days to all children with diarrhea (152). We interpret the WHO recommendation as an endorsement to give zinc to children in developing countries and have formulated our recommendation accordingly. Because zinc excess should be avoided, and because dosages in children without malnutrition have not been defined, further work is needed to establish

whether zinc supplementation also will be of benefit to all children, malnourished and well nourished alike.

Folic Acid Folic acid is not recommended for the management of children with AGE (II, B).

It has been suggested that folic acid is effective in the treatment of acute diarrhea in children (153). However, a recent well-designed double-blind RCT in 106 boys ages 6 to 23 months found no difference between folic acid and placebo in the treatment of acute watery diarrhea (154).

Glutamine Glutamine is not recommended in the management of children with AGE (II, B).

The rationale for using glutamine in the treatment of AGE is based on the assumption that glutamine is an important fuel for rapidly dividing cells, such as enterocytes and lymphocytes. Exogenous glutamine supplementation in catabolic states preserves intestinal mucosal structure and function, decreases bacterial translocation, and supports normal immunologic responses.

One RCT (155) involving 128 otherwise healthy children ages 6 to 24 months with acute diarrhea of less than 10 days duration found that the mean duration of diarrhea in the glutamine-treated group (0.3 g/kg/day for 7 days) was significantly shorter than that in the placebo group (3.40 ± 1.96 days vs 4.57 ± 2.48 days, respectively; $P = 0.004$). There were no other significant differences between the groups. See also *ORS + Glutamine*.

Nitazoxanide

There is not sufficient evidence to recommend nitazoxanide in the management of children with rotavirus-induced AGE (II, B).

Nitazoxanide is a broad-spectrum anti-infective drug that has been used against parasites and against rotavirus in cell culture. One RCT (156) in 38 children (ages 5 mo–7 y) with severe rotavirus diarrhea showed that administration of 7.5 mg/kg oral suspension nitazoxanide or placebo twice a day for 3 days results in the reduction of the median time to resolution of illness (31 h, interquartile range 22–73 for the nitazoxanide-treated group compared with 75 h, 51–124 for the placebo group; $P = 0.0137$). Nitazoxanide had no major adverse effects. It was concluded that in children with rotavirus gastroenteritis, nitazoxanide significantly reduces the duration of illness in hospitalized pediatric patients. Study limitations included a small number of subjects and possible undetected intestinal infections or comorbidities. Availability and costs may vary in European countries, which may limit the use of this drug.

Anti-infective Therapy

Anti-infective therapy should not be given to the vast majority of otherwise healthy children with acute gastroenteritis (Vb, D).

Regardless of the etiologic microorganism, which is seldom known on admission, AGE is usually self-limited. Even without specific antimicrobial therapy, clinical recovery frequently occurs within a few days and the causative organism is excreted in a relatively short time, usually a few days or weeks. Complications are uncommon. The relative prevalence of the specific enteric pathogens depends on several factors: season, climate, age, breast-feeding, day-care center attendance, and living conditions. Epidemiology is discussed elsewhere in this document.

Antimicrobial Therapy of Bacterial Gastroenteritis

Antibiotic therapy for acute bacterial gastroenteritis is not needed routinely, but only for specific pathogens or in defined clinical settings (Vb, D).

Antibiotic therapy is contraindicated in some conditions.

The goals of antibiotic therapy in children with bacterial gastroenteritis are: to improve clinical symptoms (duration of diarrhea, vomiting, fever, and abdominal cramps); to prevent complications; and to eradicate enteric pathogensin to reduce transmission. Although one would expect antibiotics to which the causative agent is susceptible in vitro to be clinically efficacious, this is not the case. For reasons that are not completely clear, in vitro susceptibility does not necessarily mean clinical efficacy. Therefore, therapeutic recommendations regarding antibiotic treatment of acute bacterial gastroenteritis must be based on the results of clinical studies. Thus far, there is almost no evidence that antibiotics are effective in bacterial gastroenteritis, with a few exceptions that are indicated below.

Pathogen-based Approaches

Shigella Gastroenteritis Antibiotic therapy is recommended for culture-proven or suspected shigellosis (II, B).

Several well-designed studies have shown that appropriate antibiotic treatment of *Shigella* gastroenteritis significantly reduces the duration of fever, diarrhea, and fecal excretion of the pathogen, and thus the infectivity (157), which is important in children attending day-care centers, children in institutions, and hospitalized children. Of note, man is the only source of *Shigella.* Antibiotic treatment is expected to reduce the risks of complications, including the risk of hemolytic-uremic syndrome associated with *S dysenteriae* infection (158).

The major problem, however, is the increasing worldwide resistance of *Shigella* to antibiotics. Therefore, *Shigella* isolates should be tested for susceptibility and local resistance patterns closely monitored. At present, effective antibiotic agents for shigellosis include third-generation cephalosporines (159–162), azithromycin (163,164), nalidixic acid, and fluoroquinolones (164,

TABLE 6. *Antimicrobial agents for the treatment of shigellosis in children*[*]

Antimicrobial agent	Route	Total daily dose	No. of doses/day	Duration
Ampicillin	PO, IV	100 mg/kg	4	5 d
Azithromycin	PO	day 1: 12 mg/kg	1	5 d
		day 2–5: 6 mg/kg	1	
Cefixime	PO	8 mg/kg	1	5 d
Ceftriaxone	IM, IV	50 mg/kg	1	2–5 d
Nalixic acid	PO	55 mg/kg	4	5 d
Trimethoprim/sulfamethoxazole[†]	PO	10/50 mg/kg	2	5 d

PO = orally; IV = intravenous; IM = intramuscular.
[*] The antimicrobial agent of choice depends on local susceptibility data.
[†] In most countries the agent is approved for infants older than 2 or 3 months.

165). Because of the high worldwide resistance, trimethoprim-sulfamethoxazole and ampicillin are recommended *only* if the strain isolated is susceptible, or if current local microbiological data suggest susceptibility.

The first-line oral empiric treatment recommended for *Shigella* gastroenteritis is azithromycin, which was found to be more effective than either cefixime or nalidixic acid (163,164), probably because of its capacity to penetrate infected cells. Alternatively, nalidixic acid or cefixime can be administered, both for 5 days. When the *Shigella* isolates are susceptible to trimethoprim-sulfamethoxazole and/or ampicillin (eg, in an outbreak setting), these agents are the recommended first-line treatment. Oral fluoroquinolones can be used in children younger than 17 years when no other alternative is feasible.

The recommended first-line parenteral treatment is ceftriaxone for 5 days (166). Two doses of ceftriaxone can be given to patients without underlying immune deficiency or bacteremia who are fever-free after 2 days of ceftriaxone treatment (167). Table 6 lists the antimicrobial agents used to treat *Shigella* gastroenteritis, their dosage, and their duration of treatment.

Salmonella Gastroenteritis Antibiotics should not be used in an otherwise healthy child with *Salmonella* gastroenteritis, because they may induce a state of healthy carrier (I, A).

Antibiotics are suggested in high-risk children to reduce the risk of bacteremia and extraintestinal infections (Vb, D). These include children with underlying immune deficiency, anatomical or functional asplenia, corticosteroid or immunosuppressive therapy, inflammatory bowel disease, or achlorhydria, and neonates or young infants (<3 months).

A Cochrane systematic review has shown that antibiotic therapy of *Salmonella* gastroenteritis does not significantly affect the duration of fever or diarrhea in otherwise healthy children or adults, when compared with placebo or no treatment (168). It resulted in more negative stool cultures during the first week of treatment, but more positive stool cultures after 3 weeks and more frequent relapse rates (vs no treatment).

Campylobacter *Gastroenteritis* Antibiotic therapy for *Campylobacter* gastroenteritis is recommended mainly for the dysenteric form and to reduce transmission in day-care centers and institutions. It may reduce symptoms if instituted within 3 days after disease onset (II, B).

A meta-analysis of 11 double-blind, placebo-controlled trials showed that antibiotic treatment of gastroenteritis caused by *Campylobacter* spp reduces the duration of intestinal symptoms by 1.3 days (169). The effect was more pronounced if treatment was started within 3 days of illness onset (169) and in children with *Campylobacter*-induced dysentery vs placebo (170). Several studies have shown that antibiotic treatment of gastroenteritis significantly reduces the duration of fecal excretion of *Campylobacter* spp and thus its infectivity, can stop an ongoing outbreak of *Campylobacter* gastroenteritis in a day-care center, and may reduce the relapse rate (170,171). It is unclear whether antibiotic treatment of *Campylobacter* gastroenteritis prevents the development of postinfectious Guillain-Barre syndrome.

Diarrheagenic Escherichia coli Antibiotic treatment of diarrhea induced by Shiga toxin–producing *E coli* (STEC), also called enterohemorrhagic *E coli*, does not significantly affect the clinical course or the duration of fecal excretion of the pathogen. After conflicting results, a meta-analysis concluded that it is currently unclear if antibiotic treatment of Shiga toxin–producing *E coli* gastroenteritis affects the risk of developing hemolytic-uremia syndrome (172). Antibiotic treatment of gastroenteritis caused by enterotoxigenic or enteropathogenic *E coli* significantly shortens the clinical course (mainly the duration of diarrhea) and fecal excretion of the pathogen (173,174). In adults, treatment of enteroaggregative *E coli* gastroenteritis by the nonabsorbed, oral antibiotic rifaximin significantly reduces the duration of diarrhea (175).

Other Causes of Bacterial Gastroenteritis Appropriate antibiotic treatment of cholera reduces significantly the durations of diarrhea and fecal shedding of *Vibrio cholerae*. The treatment of choice is doxycycline;

alternative treatment for children younger than 8 years is trimethoprim-sulfamethoxazole.

Antibiotic-associated diarrhea is usually caused by *Clostridium difficile*. Generally, withdrawal of the antibiotic is associated with prompt remission of symptoms. However, for moderate or severe disease, the first-line treatment is oral metronidazole; oral vancomycin is reserved for resistant strains. Limited data are available regarding the efficacy of antibiotics for gastroenteritis caused by *Yersinia* spp, which is recommended for bacteremia or extraintestinal infections caused by these pathogens. Antibiotic therapy is usually not needed for the uncommon cases of gastroenteritis caused by noncholera *Vibrio* spp, *Aeromonas* spp, or *Plesiomonas shigelloides*.

Empiric Antibiotic Therapy in Sporadic Cases of AGE

The cause of sporadic AGE is usually not known at presentation. The classification of these cases into invasive (or inflammatory) and watery (or noninvasive) helps us to decide whether or not to start empiric antibiotics.

1. Antibiotics may be considered for the treatment of severe invasive diarrhea. Invasive (inflammatory) gastroenteritis is defined as acute onset of bloody/mucous diarrhea (or fecal polymorphonuclear leukocytes when the examination is available) with high fever. The common causes are *Shigella* spp, *Campylobacter* spp, and *Salmonella enterica*. It is important to treat hospitalized children and children attending day-care centers to reduce transmission of *Shigella* and *Campylobacter*. The choice of the antimicrobial agent depends on the local prevalence of the 3 pathogens and the resistance patterns, as discussed above (Vb, D).
2. Watery diarrhea. Antibiotic therapy is not recommended unless the patient recently has traveled or may have been exposed to cholera (VB, D).
3. Bloody diarrhea with low or no fever, which is typical of Shiga toxin–producing *E coli*, but can be mild shigellosis or salmonellosis. Antibiotics are not recommended unless epidemiology suggests shigellosis (Vb, D).

Parenteral rather than oral antibiotic therapy is recommended (Vb, D) for:

1. Patients unable to take oral medications (vomiting, stupor, etc).
2. Patients with underlying immune deficiency who have AGE with fever.
3. Severe toxemia or suspected bacteremia.
4. Neonates and young infants (<3 months) with fever. Sepsis work-up and antibiotics should be considered according to local protocols.

Antimicrobial Therapy of Extraintestinal Infections of Enteric Pathogens

Occasionally enteric bacterial pathogens can cause extraintestinal infections, including bacteremia of focal infections. These infections should be treated with antibiotics, usually parenterally. Carrier state after AGE is uncommon in children; there are no data to support the efficacy of antibiotics in these children.

Antimicrobial Therapy of Parasite-induced Gastroenteritis

The parasites that most often cause diarrhea are *Cryptosporidium* and *Giardia*, although the direct role of the latter is uncertain in European countries. Infection by *Cryptosporidium* is common in the first 2 years of life, and symptoms are usually mild and do not require diagnostic or therapeutic intervention. *Cryptosporidium* may be responsible for acute self-limiting diarrhea in immunocompetent children (176). *Cryptosporidium* is the most important enteric opportunistic agent in AIDS. Immunocompromised children can have severe diarrhea, which may result in malnutrition and severe dehydration. A Cochrane metanalysis (177) confirms the absence of evidence for effective agents in the management of cryptosporidiosis. The results indicate that nitaxozanide reduces the load of parasites and may be useful in immunocompetent individuals. A 3-day course of nitazoxanide oral suspension has been approved by the US Food and Drug Administration for treatment of children 12 months of age or older. Given the severity of *Cryptosporidium* infection in immunocompromised individuals and the potential to improve compliance by decreasing nausea and vomiting, nitaxozanide is worth considering in immunocompromised patients.

Giardia has been detected at a frequency as high as 8% to 10% in healthy carriers (178,179). Therefore, the direct role of *Giardia* as an enteric pathogen is not proved. Because microbiological investigation is not required unless the symptoms are severe or persistent, *Giardia* is expected to be detected in unusual cases, and treatment should be considered when other agents are not detected. The drugs of choice are metronidazole, tinidazole, or nitazoxanide (180,181). A 3-day course of nitazoxanide oral suspension is as effective as metronidazole, and has the advantage of treating multiple other intestinal parasites. The treatment of asymptomatic carriers is not recommended.

Entamoeba histolytica also can cause diarrhea. Although amebiasis is not a common problem in European countries, all patients with bloody diarrhea who have traveled to, or are from, endemic areas should be tested for amebiasis. Treatment always should include a luminal amebicide such as iodoquinol, paramomycin, or

diloxanide to eradicate colonization, prevent spread, and/or reduce the risk of invasive disease. Patients with intestinal symptoms or extraintestinal disease should be treated with metronidazole or tinidazole before the therapeutic course of luminal amebicide (181).

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PREVENTION

For the table of evidence referring to the topics of this section, see Table 6.1 in Appendix 2.

Vaccines

Vaccines are available against rotavirus (1,2) but not for the other common causes of AGE. The Vesikari et al guidelines (3), which were developed in parallel to the present guidelines and are in this supplement, provide an excellent update of rotavirus vaccines. Vaccines for *Shigella* spp, enterotoxigenic *E coli*, and *C jejuni* are in advanced stages of development.

Passive Prevention or Therapy

There is evidence that passive prevention by immune globulin or hyperimmune colostrums may be beneficial for GE induced by rotavirus (4,5), enteropathogenic and enterotoxigenic *E coli* (6), or *Shigella* (7). The routine use of immune globulins is not recommended.

Chemoprophylaxis

Chemoprophylaxis by antimicrobial agents has limited efficacy in traveler's diarrhea in adults. Because no data are available in children, and given the increasing antibiotic resistance of enteric pathogens, routine chemoprophylaxis is not recommended. Chemoprophylaxis can be considered in specific individuals (immunocompromised children) or settings (to control an outbreak).

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Conflicts of Interest of Working Group Members

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APPENDIX 1: SEARCH STRATEGIES

Definition

Articles were identified by searching the MEDLINE database (1966–2006) via the PubMed search engine, EMBASE (1980–2006), and the Cochrane Database of Systemic Reviews (1988–2006). We used search strings to identify studies on the age group, a previously reported string for trials (1), MeSH terms and text words related to the disease, and specific key questions/keywords.

Search String

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ''clinical trial'' [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind [tw])) OR (''latin square'' [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])) AND (''Child, Preschool'' [MeSH] OR ''Infant''[MeSH:NoExp] OR ''Infant, Newborn''[MeSH:NoExp] OR child* [tw] OR infant* [tw] OR newborn* [tw] OR neonate* [tw]).

This string was combined, using Boolean AND, to disease, key questions, and keywords specific to each item allocated to us.

Key Words

*definition of diarrhea, children, child**

Inclusion Criteria

1. Studies in English.
2. Previously healthy children ages 5 years or less with clinically diagnosed gastroenteritis.
3. Randomized controlled trial OR clinical trial OR comparative study OR evaluation studies OR follow-up studies OR prospective study OR cross-over studies.
4. Trials on humans NOT animals.

Exclusion Criteria

1. Studies published as abstracts, letters, or personal communications.
2. Risk factors for acute or persistent or severe diarrhea (for Section 7).
3. Studies on children with oncological disease.
4. Studies on appendicitis, *Clostridium difficile* colitis, inflammatory bowel disease, esophagitis, gastritis, or necrotizing enterocolitis.

Papers identified/included: 92 identified/5 fulfilled the inclusion criteria.

Epidemiology

For details refer to *Search Strategy for the Definition of Diarrhea*.

Key Words

acute diarrhea, acute diarrhoea, acute gastroenteritis, epidemiology, frequency, etiology, enteric pathogens, infectious agents, agents of AGE, seasonal distribution, geographical distribution.

Papers identified/included: 2825 identified/6 European trials fulfilled the inclusion criteria.

Risk Factors for Severe and/or Persistent Disease

For details refer to *Search Strategy for the Definition of Diarrhea*.

Key Words

severe diarrhea, severity of diarrhea, severe gastroenteritis, hospitalized diarrhea, dehydrating diarrhea, persistent diarrhea, death for diarrhea AND *age group, child age, geography, rural area, urban area, high income, low income, etiology, clinical features, clinical manifestation, vomiting, blood in stools, hospitalization, hospitalisation, nosocomial infection, intensive care unit, socioeconomic status, socioeconomic factors, behaviour, environmental factors, maternal age, maternal knowledge, risk factors, feeding, breast-feeding, formula feeding, feeding status, feeding practice, siblings, other children under-five years, nursery, day care, risk factor for day care, malnutrition, undernutrition, nutritional condition, nutritional state, underweight, stunted, wasted, underlying chronic diseases, immune disease, immune deficiencies, immunodepression, chronic disease, comorbidity.*

Articles identified/included: Age: 163 identified/10 included. Geography: 22 identified/none fulfilled the

inclusion criteria. Etiology: 253 identified/10 included. Clinical features: 137 identified/6 included. Hospitalization: 84 identified/2 included. Socioeconomic factors: 171 identified/18 included. Feeding: 653 identified/19 included. Siblings: 2 identified/1 included. Nursery or day care: 30 identified/4 included. Nutritional condition: 536 identified/28 included. Chronic or immune diseases and comorbidity: 776 identified/15 included.

Clinical Evaluation and Disease Severity

We systematically reviewed the literature on ''Are clinical symptoms related to the etiology of diarrhea?'' and ''How to assess the severity of diarrhea: what is the reliability of symptoms and scores to estimate the degree of dehydration?''

Articles were identified by searching the MEDLINE database (1966–January 2007), The Cochrane Library, and the Science Citation Index. We used MeSH terms (using the explode command that captures all terms under the specific MeSH term), related to the disease and specific key questions, and we also searched for text words. We found 1 good quality systematic review, and we used the Science Citation Index to identify 1088 articles citing this review and key publications.

Inclusion Criteria

1. Previously healthy children with clinically diagnosed gastroenteritis.
2. Reporting on symptoms related to severity of etiology of diarrhea.
3. Studies on humans NOT animals.

Exclusion Criteria

1. Studies published as abstracts, letters, or personal communications.
2. Studies only reporting on laboratory investigations.
3. Studies on children with oncological disease.
4. Studies on appendicitis, *Clostridium difficile* colitis, inflammatory bowel disease, esophagitis, gastritis, or necrotizing enterocolitis.

Key Words

Definition of the disease or symptoms: *exp Diarrhea/, diarr$.mp.[mp=title, original title, abstract, name of substance word, subject heading word], exp colitis/ or exp dysentery/ or exp enteritis/ or exp enterocolitis/.*

Children: *exp Child/, exp Infant/, child$.mp., infant$.mp., (paediatri$ or pediatri$).mp.*

Risk factors or symptoms: *no limitation or definition,* this strategy catches all.

Diagnostic studies: *exp ''Sensitivity and Specificity''/, sensitiv$.mp., accura$.mp., predict$.mp.*

Etiologic agents: *exp ''bacterial infections and mycoses''/, exp virus diseases/, exp parasitic diseases/*

Papers identified/included: Clinical symptoms: 1170 identified/11 fulfilled the inclusion criteria. Severity/dehydration: 1088 identified/7 fulfilled the inclusion criteria.

Indications for a Medical Visit and for Hospital Admission

For details refer to *Search Strategy for the Definition of Diarrhea*.

Key Words

acute diarrhea, acute diarrhoea, acute gastroenteritis, age, risk factors for diarrhea, bicarbonate, basis excess, dehydration, sodium, urea, serum electrolyte, electrolyte panel, indication for hospitalization, hospital∗*, admission, telephone consultation, telephone triage, hospital referral, discharge.*

Papers identified/included: 272 identified/21 included.

Hygiene Precautions—Indications for Isolation

Key Words

acute diarrhea, acute diarrhoea, acute gastroenteritis, isolation precaution, isolation measures, physical measures, biological measures.

Papers identified/included: 75 identified/5 fulfilled the inclusion criteria. *The Red Book* 2006, American Academy of Pediatrics, 27th edition, was consulted.

Diagnostic Workup

Articles were identified by direct search of the MEDLINE database via the PubMed search engine. The keywords used for the first and most broad search strategy were *acute gastroenteritis* or *acute diarrhea*. All searches were limited by age (all children 0–18 years), publication date (January 1966–December 2006), English language articles, and human studies. In addition, textbook reference lists, reviews, editorials, comments, expert opinions, and articles from the collections of experts in the field were reviewed and secondary searches for additional articles were made within the bibliographies of the reviewed articles. These searches produced 6779 articles. This preliminary search was reduced using keywords specific to the diagnostic workup and nutritional management sections.

Key Words

urea or *BUN* or *BUN/creatinine* or *bicarbonate* or *anion gap* or *base excess/deficit* or *serum pH, electrolytes* or *natrium/sodium* or *potassium* and *diagnostic value* or *yield* or *sensitivity* or *specificity* or *positive predictive value* or *negative predictive value* and *acute gastroenteritis* or *acute diarrhea* or *dehydration, leukocytosis or white blood cells count or C-reactive protein and diagnostic value* or *yield* or *sensitivity* or *specificity* or *positive predictive value* or *negative predictive value* and *acute gastroenteritis* or *acute diarrhea, stool cultures* or *rapid stool tests* or *fecal occult blood* or *fecal lactoferrin* or *fecal leukocytes* or *fecal calprotectin* and *diagnostic value or yield* or *sensitivity* or *specificity* or *positive predictive value* or *negative predictive value* and *acute gastroenteritis* or *acute diarrhea, endoscope* or *histology* and *acute gastroenteritis* or *acute diarrhea* and *diagnostic value* or *yield or sensitivity* or *specificity* or *positive predictive value* or *negative predictive value.*

Laboratory tests, including urea or BUN or BUN/creatinine or bicarbonate or anion gap or base excess/deficit or serum pH, electrolytes or natrium/sodium or potassium, leukocytosis and serum C-reactive protein. The studies included were all prospective, controlled trials, published in peer-reviewed journals. No prospective studies on leukocyte count diagnostic value or yield were identified. Therefore, for this subject the retrospective studies in children and adults are detailed in the text.

Papers identified/included: 160 identified/13 included.

Rapid stool tests, including fecal occult blood, fecal lactoferrin, fecal leukocytes, fecal calprotectin, and indications for stool cultures. The studies included were all peer-reviewed journal articles, prospective trials (controlled trials when identified), not reviews, meta-analysis, systematic reviews, editorials, except as sources for additional bibliographic references). Similar exclusion criteria were applied for this search.

Papers identified/included: 103 identified/7 were included.

Because no relevant study was published after the comprehensive meta-analysis by Gill et al (2), this was the only source of information in these guidelines. This meta-analysis included studies in both adults and children, but the analysis was performed separately for developed and developing countries.

Endoscopy and histology: All of the identified studies, either prospective or retrospective, were from adults and were descriptive. The few studies from adults were performed mainly to identify histological criteria able to differentiate between acute and chronic colitis.

Exclusion Criteria

1. Studies published as abstracts, letters, personal communications.
2. Studies in malnourished children or prolonged diarrhea.
3. Studies of *Clostridium difficile* colitis.
4. Studies on oral rehydration.

Rehydration and Pharmacological Therapy

A systematic review was conducted to identify evidence on treatment (rehydration and drug therapy). The following electronic databases were systematically searched: MEDLINE (1966–January 2006), EMBASE (1980–January 2006), The Cochrane Database of Systematic Reviews (Issue 4, 2006), and The Cochrane Controlled Trials Register (Issue 4, 2006) for RCTs and quasi-randomized controlled trials (ie, allocating participants according to date of birth, the number of hospital records, etc) that compared treatment options with placebo or no additional intervention. The participants had to be infants and children up to 18 years of age with acute gastroenteritis, who were treated in hospitals or as outpatients. The search strategy included use of a validated filter for identifying controlled trials (1), which was combined with general terms related to gastroenteritis (gastroenteritis, diarrhoea/diarrhea, diarrh*, infant*, child*, toddler*) together with topic-specific strategy. The primary outcome measures were duration of diarrhea (number of hours) and stool output (+ intervention specific). The secondary outcome measures were as follows: stool frequency, vomiting, adherence (acceptance of the treatment), and adverse effects. Additionally, all outcomes specific to given intervention were evaluated.

Included and Excluded Studies

The reviewers independently screened titles and abstracts identified according to the above-described search strategy. All potentially relevant articles were retained, and the full text of these studies was examined to determine which studies satisfied the inclusion criteria. The same reviewers independently carried out data extraction, using standard data extraction forms. Studies reported in languages other than those familiar to the authors were translated. Discrepancies between the reviewers' findings were resolved by discussion. No limit was imposed regarding the language of publication, but certain publication types (ie, letters to the editor, abstracts, and proceedings from scientific meetings) were excluded.

Study Quality

For RCTs, reviewers assessed the quality of studies that met the inclusion criteria. Use of the following strategies associated with good quality studies was assessed: generation of allocation sequences and allocation concealment; blinding of the investigators, participants, outcome assessors, and data analysts (yes/no/not reported); intention-to-treat analysis (yes/no); and comprehensive follow-up. Generation of allocation sequences was considered adequate if the resulting sequences were unpredictable (eg, computer generated random numbers, table of random numbers, drawing lots or envelopes, throwing dice). Conversely, it was considered inadequate if the resulting sequences were predictable (eg, according to case record number, date of birth, date of admission, alternation). Allocation concealment was considered adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before enrollment of eligible participants in the study. However, the quality of the allocation concealment was considered unclear when randomization was used but no or inadequate information about the method was available and when inappropriate methods of randomization (eg, alternate medical record numbers, unsealed envelopes, open allocation schedule) were used. In regard to the intention-to-treat analysis, an answer of ''yes'' meant that the authors had specifically reported undertaking this type of analysis and/or that our own study confirmed this finding. Conversely, a ''no'' meant that authors did not report use of intention-to-treat analysis and/or that we could not confirm its use on study assessment. To evaluate the completeness of patient follow-up, we determined the percentage of participants excluded or lost to follow-up.

Papers identified/included: 276 identified/60 were included.

Nutritional Management

Inclusion Criteria

1. Peer-reviewed journal articles.
2. Randomized controlled trials (or controlled trials in which RCT not identified or randomization not specified).

Exclusion Criteria

1. Studies published as abstracts, letters, personal communications.
2. Studies in malnourished children or prolonged diarrhea.
3. Studies of *Clostridium difficile* colitis.
4. Studies on oral rehydration.

Key Words

feeding, refeeding or *re-feeding*, *early feeding* or *early refeeding* or *early re-feeding, late feeding* or *late refeeding* or *late re-feeding, breast-feeding, formula feeding* or *formula refeeding* or *formula re-feeding, soy formula, lactose free formula* or *lactose-free formula, cow's milk, elimination diet, hydrolyzed formula, diluted feeding* or *diluted formula, full-strength feeding* or *full strength formula, fruit juice, solid food, mixed diet, BRAT, cereal, starch, rice.*

Papers identified/included: 118 identified/40 fulfilled the inclusion criteria. Several important reviews on the subject are also detailed.

Anti-infective Therapy

We searched articles through the MEDLINE database (January 1966–December 2006) limited for human studies only and for children (0–18 years). In addition to the original articles, we read carefully the reviews, editorials, and expert opinions identified by this search. Publications such as abstracts only or letters were excluded. We looked for all the outcomes examined. Thirty-six publications were found.

In the next phase, we looked for specific bacterial pathogens and selected all articles that examined antibiotic treatment of these pathogens. Because sometimes data were available only for adults, we looked for all human studies. In all, 1128 publications were found. We also examined the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the National Guidelines Clearing House for the same key words as above. Fourteen relevant publications were found.

Key Words

The first broad search strategy used *acute gastroenteritis* or *acute diarrhea* and treatment, or anti?bacterial* or anti?microbial* as key words. Second phase: shigell*, salmonell*, campylobacter, enterotoxigenic *E. coli*, enterohemorrhagic *E. coli*, enteropathogenic *E. coli*, enteroaggregative *E. coli.*

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