European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe: Update 2014

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ABSTRACT

Objectives: These guidelines update and extend evidence-based indications for the management of children with acute gastroenteritis in Europe.

Methods: The guideline development group formulated questions, identified data, and formulated recommendations. The latter were graded with the Muir Gray system and, in parallel, with the Grading of Recommendations, Assessment, Development and Evaluations system.

Results: Gastroenteritis severity is linked to etiology, and rotavirus is the most severe infectious agent and is frequently associated with dehydration. Dehydration reflects severity and should be monitored by established score systems. Investigations are generally not needed. Oral rehydration with hypoosmolar solution is the major treatment and should start as soon as possible. Breast-feeding should not be interrupted. Regular feeding should continue with no dietary changes including milk. Data suggest that in the hospital setting, in non–breast-fed infants and young children, lactose-free feeds can be considered in the management of gastroenteritis. Active therapy may reduce the duration and severity of diarrhea. Effective interventions include administration of specific probiotics such as *Lactobacillus* GG or *Saccharomyces boulardii*, diosmectite or racecadotril. Anti-infectious drugs should be given in exceptional cases. Ondansetron is effective against vomiting, but its routine use requires safety clearance given the warning about severe cardiac effects. Hospitalization should generally be reserved for children requiring enteral/parenteral rehydration; most cases may be managed in an outpatients setting. Enteral rehydration is superior to intravenous rehydration. Ultrarapid schemes of intravenous rehydration are not superior to standard schemes and may be associated with higher readmission rates.

Conclusions: Acute gastroenteritis is best managed using a few simple, well-defined medical interventions.

Key Words: acute gastroenteritis, child, children, definition of diarrhea, guidelines

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These guidelines are intended to provide a general indication and not as a definitive basis for diagnosis or treatment in any particular case.

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1. BACKGROUND

In 2008, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Society of Pediatric Infectious Diseases (ESPID) jointly developed evidence-based guidelines for the management of acute gastroenteritis (AGE) in children for practitioners at all levels of health care—primary care physicians, pediatricians, and family physicians—in Europe (1). The guidelines have had a major impact on the management of gastroenteritis as judged by the number of citations (a total of 160) and by several articles addressing their quality and impact (2,3). In addition, an e-learning program was created to implement their application.

We have now updated the guidelines to take account of the evidence accumulated over the last 5 years. The update differs from the original guidelines in that we have rated the quality of evidence

and the weight of recommendations using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system, which has advantages over other rating systems (4). To reflect the changes that have occurred, we have, however, retained, or wherever appropriate, revised, the Muir Gray rating that we used 5 years ago (see ''Methods for Guidelines Update Development''). Another novelty is a section on the management of children in hospital. This section addresses crucial issues in the management of diarrhea, namely, enteral and parenteral rehydration, correction of hydroelectrolyte imbalance, complications, and monitoring the course of the disease.

As in the case of the 2008 AGE guidelines, the tables of evidence are an integral part of the update. Interested readers can access this material, which was used to produce the recommendations, in the online version of the *Journal of Pediatric Gastroenterology and Nutrition* (*www.jpgn.org*).

2. METHODS FOR GUIDELINES UPDATE DEVELOPMENT

We applied the same approach we had used to develop the previous guidelines (see the 2008 guidelines for details). In brief, the process started with specifying clinical questions that define the population for search purposes.

These were defined as follows: previously healthy children ≤5 years of age with clinically diagnosed AGE (diarrhea and/or vomiting presumably of infectious origin), in- or outpatients living in geographic Europe. Children with at-risk conditions, such as chronic disorders or immunodeficiency, are not covered.

Recommendations were formulated and graded according to the Muir Gray (5) and Cook (6) (Table 1), and the GRADE system (4) (Table 2). See additional information about methods in the Online Repository.

3. 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 ≥3 in 24 hours), with or without fever or vomiting; however, a change in stool consistency versus previous stool consistency is more indicative of diarrhea than stool number, particularly in the first months of life. Acute diarrhea typically lasts <7 days and not >14 days.

4. EPIDEMIOLOGY

The incidence of diarrhea ranges from 0.5 to 2 episodes per child per year in children <3 years in Europe.

Gastroenteritis is a major reason for hospitalization in this range of age.

Rotavirus is the most frequent agent of AGE; however, norovirus is becoming the leading cause of medically attended AGE in countries with high rotavirus vaccine coverage.

The most common bacterial agent is either *Campylobacter* or *Salmonella* depending on country.

Intestinal infections are a major cause of nosocomial infection.

Hospital- and population-based studies showed that 45% to 75% of children with AGE had a pathogenic enteric organism isolated from their stools. Rotavirus is the most common cause of AGE in children in all European countries. A comprehensive literature search in Western Europe showed an incidence of rotavirus gastroenteritis as high as 1.33 to 4.96 cases/100 person year. Hospitalization rates for rotavirus gastroenteritis ranged from 7% to 81% in various countries. Nosocomial rotavirus gastroenteritis accounted for 50% to 70% of all cases of hospital-acquired gastroenteritis, and prolonged hospital stays by 4 to 12 days. This rate had a major impact on costs (7). Rotavirus serotype predominance appears to change on a seasonal basis within each country and may even differ between regions of the same country.

Two oral live rotavirus vaccines, Rotarix and RotaTeq, licensed in Europe in 2006, were found to have good safety and efficacy profiles in large clinical trials. A significant reduction of AGE-related hospital admissions has been reported in countries with a routine rotavirus vaccination program (8). Although vaccination coverage in European countries is still low, changes in AGE epidemiology have been reported after the introduction of rotavirus vaccination. In fact, the proportion of new (G12) or selected (G2P4) strains increased in countries after the introduction of vaccination (9,10).

Norovirus, generally considered the second leading agent of AGE, is fast becoming a leading cause of medically attended gastroenteritis in countries with high rotavirus vaccine coverage (11,12). Noroviruses represent 10% to 15% of causes of hospitalizations for AGE in European children, and are often associated

TABLE 1. Strength of evidence and grade of recommendations in support of the recommendations formulated in the 2008 ESPGHAN/ESPID guidelines for the management of AGE in children in Europe

Strength of evidence	
I	Strong evidence from ≥1 systematic review(s) of well-designed RCTs
II	Strong evidence from ≥1 properly designed RCT(s) of appropriate size
III	Evidence from well-designed trials without randomization, single group pre–post, cohort, time series, or matched case–control studies
IV	Evidence from well-designed trials, nonexperimental studies from >1 center or research group
Va	Opinion of respected authorities
Vb	Clinical evidence, descriptive studies, or reports of expert committees
Grade of recommendation	
A	Supported by level I evidence, highly recommended
B	Supported by level II evidence, recommended
C	Supported by level III evidence, recommended
D	Supported by level IV and level V evidence; the consensus route would have to be adopted

AGE = acute gastroenteritis; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; ESPID = European Society for Pediatric Infectious Diseases; RCT = randomized controlled trial.

TABLE 2. GRADE system

Quality of evidence	
High quality	Further research is unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is extremely likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is extremely uncertain
Grade of recommendation	
Strong	When the desirable effects of an intervention clearly outweigh the undesirable effects, or they clearly do not
Weak	When the tradeoffs are less certain (either because of the low quality of evidence or because the evidence suggests that desirable and undesirable effects are closely balanced)

GRADE = Grading of Recommendations, Assessment, Development, and Evaluations.

with a more severe pattern of diarrhea, mainly in case of infection with specific genotypes (GII4 and Bristol group) (13,14). Severe outbreaks owing to new norovirus variants were recently reported in schools and in day-care centers (15,16). Finally, norovirus is the first or second cause of AGE in traveler's diarrhea and in diarrheic patients returning from travel (16,17).

A large study in the United Kingdom revealed major changes in the etiological pattern of gastroenteritis. In fact, there was a decline of *Salmonella* and an increase in the detection of norovirus and sapovirus (18). Bacterial (mainly *Campylobacter* and *Salmonella*) and protozoan organisms are less common causes of AGE. In addition, *Clostridium difficile* infection, whose frequency is rapidly increasing worldwide, has been related to community-acquired acute diarrhea even in low-risk pediatric populations (19,20).

Giardia is rarely associated with AGE in immunocompetent children. Carriage of *Giardia* or *Cryptosporidium* in stool is low in children living in Europe, namely 1% to 3% in day-care centers (21,22). *Giardia* or *Cryptosporidium* infestation in Europe is frequently asymptomatic; however, AGE outbreaks owing to *Cryptosporidium* can occur in children with normal immunity attending day care centers (22).

Asymptomatic carriage in stools of nonpathogenic protozoa is not rare in children returning from tropical countries.

5. RISK FACTORS FOR SEVERE AND/OR PERSISTENT DISEASE

See supplemental table at *http://links.lww.com/MPG/A316*.

5.1 Is There a Relation Between Severe or Persistent Diarrhea and Etiology?

Rotavirus is the most severe enteric pathogen of childhood diarrhea (III, C) (strong recommendation, moderate-quality evidence).

In children with persistent diarrhea the main pathogens detected are as follows:

- Rotavirus, norovirus, astrovirus, enteroaggregative *Escherichia coli*, and atypical *E coli* (III, C) (weak recommendation, low-quality evidence).
- *Giardia* (I, A) (weak recommendation, moderate-quality evidence)
- *Cryptosporidium* and *Entamoeba histolytica* (III, C) (weak recommendation, low-quality evidence)

Studies confirmed that viral pathogens, mainly rotavirus, are the main cause of persistent or severe diarrhea in children in Europe, whereas parasites are the main cause in the developing world (23). In Spain, severe clinical conditions were often associated with rotavirus infections (24). In a retrospective German study, children with rotavirus infection had significantly higher severity scores, more diarrheal events, and longer-lasting diarrhea than children with norovirus or adenovirus-induced AGE (25). A prospective survey reported an incidence of 1.2/100,000 cases of extremely severe rotavirus diarrhea in Germany, which included cases of rotavirus-related encephalopathy and deaths (26).

Although norovirus may induce frequent and severe vomiting (25), norovirus and adenovirus infections are less severe than those caused by rotavirus (13,25,27,28). *Salmonella* AGE was found to be associated with more diarrheal episodes/day and longer duration of diarrhea compared with common viral infections (25). Coinfection with different pathogens is associated with a more severe course of symptoms (29).

Two studies found that parasites (*Cryptosporidium*, *Giardia*, and *E histolytica*) (30–32) and some strains of enterotoxigenic *E coli* (ETEC) (33) are important causes of persistent diarrhea in developing countries. However, no specific bacterial species was associated with persistent diarrhea in more than 1000 children in Peru (34). Therefore, it was suggested that there is not sufficient evidence to justify the routine use of antimicrobials for children with persistent diarrhea when etiology is unknown (35).

5.2 Is There a Relation Between Host-Related Factors and Risk of Severe or Persistent Diarrhea?

5.2.1 Risk Factor: Younger Age

The high incidence of dehydration in infants <6 months is related to a higher exposure to rotavirus (III, C) (weak recommendation, low-quality evidence).

In developing countries, a young age (<6 months) is related to the severity and persistence of diarrhea (II, B) (strong recommendation, low-quality evidence).

Two observational studies performed in Europe evaluated whether young age is a risk factor for specific pathogens of diarrhea (13,23). In 1 study the etiology of diarrhea differed between infants and children age >2 years as follows: viral (98% vs 44%), bacterial (23% vs 50%), and parasitic (0% vs 31%) (23). Similar findings were obtained by the other study (13).

Ten studies in developing countries (31,33,34,36–42) agreed that persistent diarrhea was more frequent in infants age <6 months.

5.2.2 Risk Factor: Feeding Practice

Predominant breast-feeding may reduce the risk of AGE in young European infants (III, C) (strong recommendation, moderate-quality evidence).

In developing areas early weaning may be associated with earlier onset of severe or prolonged diarrhea (III, C) (weak recommendation, low-quality evidence).

A prospective study conducted in Spain showed that predominant breast-feeding for 4 to 6 months reduced the risk of gastroenteritis (43), and an earlier prospective study conducted in the United States showed that breast-feeding may prevent severe episodes of diarrhea (44). Consistent and even stronger evidence of the benefits of breast-feeding has been reported in developing countries (31,32,45).

5.2.3 Risk Factor: Underlying Chronic Disease or Immune Deficiencies

Children with immune deficiencies have a higher risk of developing more prolonged and more severe disease (III, C) (weak recommendation, low-quality evidence).

Malnutrition and immunodeficiencies are risk factors for persistent parasitic diarrhea in developing countries (III, C) (weak recommendation, low-quality evidence).

C difficile is a major agent of severe diarrhea in selected chronic diseases such as inflammatory bowel disease (IBD) and oncologic conditions (III, C) (weak recommendation, low-quality evidence).

Children with immunodeficiency, underlying chronic conditions, or undergoing treatment may have a more severe and prolonged course of common diarrheal infections (eg, rotavirus or norovirus), or may be at a greater risk for contracting opportunistic infections (eg, *C difficile*, *Cryptosporidium*, *Giardia*) (46–50). *C difficile* is emerging as a major agent of severe diarrhea in children with IBD, neoplastic diseases, and other chronic conditions (19, 51, 52; references 51–222 can be viewed at *http://links.lww.com/MPG/A318*).

Highly immunosuppressed patients failed to eliminate norovirus and had a higher risk of developing persistent or chronic diarrhea (48). Similarly, prolonged antigenemia during rotavirus infection was reported in stem cell transplant recipients (49). A retrospective study on >6500 children with rotaviral or nonrotaviral AGE did not find a relation between chronic illnesses and the need for intensive care treatment (46). In children who underwent renal transplantation, *Cryptosporidium* should be suspected in this population (47).

Protein energy malnutrition, vitamin A deficiency, poor folate status, and prior antibiotic use are risk factors for persistence of diarrhea in developing countries (40,41,45,53–57).

5.3 Is There a Relation Between the Child's Clinical Condition and Risk of Severe or Persistent Diarrhea?

Loss of appetite, fever, vomiting, and mucus in stools are frequently associated with persistent diarrhea (III, C) (weak recommendation, very low-quality evidence).

Fever, severe dehydration, and lethargy, which are more common in rotavirus infection, indicate systematic involvement and are associated with severe diarrhea (III, C) (weak recommendation, low-quality evidence).

In developing countries, severe malnutrition, underlying clinical conditions, and concomitant diseases may significantly affect disease severity and clinical outcomes in children with AGE (58). In industrialized areas, the severity of AGE is reflected by the degree of dehydration; however, persistent diarrhea and systemic symptoms, which are occasionally observed in children with AGE, are associated with a worse outcome.

Data on the relation between specific general features and the risk of severe AGE may be extrapolated from observational studies. The presence of high-grade fever and severe dehydration, as well as the association of fever and lethargy with typical gastrointestinal symptoms, probably indicates severe rotavirus-associated AGE (59,60). Rotaviral AGE is associated with a higher risk of metabolic disorders, particularly hypoglycemia (46). Benign afebrile seizures, not related to severe dehydration or electrolyte imbalance, have been associated with viral (rotavirus and norovirus) gastroenteritis (61–64). A considerable number of encephalopathies were reported in a surveillance study in approximately 100 cases of extremely severe diarrhea (26). In a retrospective controlled trial of nontyphoid *Salmonella* gastroenteritis, children with diarrhea who appeared toxic or presented seizures at hospital admission were more likely to have bacteremia than those with isolated gastrointestinal symptoms (65). The severe consequences of these data support the strong recommendation, although the quality of evidence is low.

5.4 Is There a Relation Between Setting or Socioeconomic Factors and Risk of Severe or Persistent Diarrhea?

Children attending day care centers have a greater risk of mild and severe diarrheal illness than children at home (III, C) (weak recommendation, low-quality evidence).

In European countries, there is evidence, although weak, of a link between low socioeconomic status and the severity or persistence of diarrhea (III, C) (weak recommendation, very low-quality evidence).

Setting (hospital or day care) and socioeconomic factors may affect the course of AGE because they are associated with increase exposure to enteric pathogens and to risk of severe or protracted diarrhea. The risk of nosocomial diarrhea is related to young age and increases with duration of hospitalization; it may reach 70% in young children staying in hospital for 6 days (7,66,67). The incidence rate of nosocomial AGE decreased with age (26%–48% in the first year of life, and 2% to 7% at 24 months) (68), and mortality due to nosocomial rotavirus AGE may be higher in children under 12 months of age than in children older than that age (7). Nosocomial cases tended to be less severe than community-acquired cases (69), and can be easily prevented by adherence to hand-hygiene measures (70).

Children attending day care can be easily infected by rotavirus (71). Stringent hygiene measures (including diaper changing, hand washing, alcohol-based hand sanitizer, and food-preparation equipment) may, however, reduce this risk (72,73).

Two studies on the impact of low socioeconomic status (estimated using standardized deprivation indices) on hospital admission for AGE in UK children produced conflicting results (74,75).

6. CLINICAL EVALUATION AND DISEASE SEVERITY

6.1 What Are the Indications for a Medical Visit?

A telephone triage can be appropriate in the management of uncomplicated AGE or to evaluate the need for a medical visit (Vb, D) (weak recommendation, low-quality evidence).

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

- Age <2 months (III, C) (strong recommendation, low-quality evidence)
- Severe underlying disease (eg, diabetes and renal failure) (Vb, D) (strong recommendation, very low-quality evidence)
- Persistent vomiting (III, C) (strong recommendation, low-quality evidence)
- High-output diarrhea with elevated stool volumes (>8 episodes/day) (III, C) (strong recommendation, low-quality evidence)
- Family-reported signs of severe dehydration (Vb, D) (strong recommendation, very low-quality evidence)

AGE in European countries is generally a relatively mild and self-limiting condition, although it may occasionally evolve into a serious illness. Most cases may be managed at home. Caregivers should be encouraged to have oral rehydration solution (ORS) at home and start administering it as soon as AGE symptoms begin in order to reduce complications and the need for a medical visit.

A telephone consultation can be appropriate in the management of uncomplicated cases of AGE (76). The aim of a telephone consultation is to obtain sufficient information to enable the physician to estimate the child's clinical condition and the risk of dehydration. Questions to caregivers should be specific and easy to understand, and should focus on the following:

- The child's age
- The child's risk factors
- Recent medical history
- 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
- Whether the child is able to receive oral fluids
- Urine output and hydration state
- The child's neurological condition.

Infants 2 to 3 months old, although at a relatively low risk of diarrhea, may be at a higher risk of dehydration and complications, and may need a medical visit. A comparison of AGE guidelines published up to 2011 showed a significant consistency in the recommendations for medical consultation during childhood AGE (3); however, other guidelines indicated family reliability as a prerequisite for home management and included ''reported signs of severe dehydration'' as an indication for a medical visit (77–79).

6.2 How Is Dehydration Assessed?

The best measure of dehydration is the percentage loss of body weight (Vb, D) (weak recommendation, low-quality evidence).

Historical points are moderately sensitive as a measure of dehydration (III, C) (weak recommendation, moderate-quality evidence).

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

Parental reports of dehydration symptoms are so low in specificity that they may not be clinically useful; however, parental report of normal urine output decreases the likelihood of dehydration (Vb, C) (strong recommendation, low-quality evidence).

Little is known about the severity of diarrhea and/or vomiting and dehydration in industrialized countries; therefore, recommendations are largely based on data from developing countries. In the latter, infants and young children with frequent high-output diarrhea and vomiting are most at risk (III, C) (weak recommendation, low quality evidence).

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

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

Classification of dehydration into no, mild-to-moderate, or severe is typically based on pre- and postillness weight. Postillness weight gain is considered the criterion standard for the assessment of the severity of dehydration. Pruvost et al (80), however, recently questioned the value of body weight measurement to assess dehydration in children.

Scoring Systems to Assess Dehydration and Severity of Illness

The performance of scoring systems depends on settings and the operator. There is no single standard method. Rather, the latter derives from a compromise between accuracy and reliability on one side, and operators and setting on the other. It seems reasonable that different scoring systems are used in outpatient and inpatients.

Although dehydration is the major determinant of severity of AGE, it is not the only one. Several scoring systems assess dehydration based on clinical signs and symptoms (eg, capillary refill, skin turgor, urinary output) (dehydration scales). Other scores evaluate the global clinical features based on a cluster of symptoms (eg, diarrhea, vomiting, fever) and the need of hospital stay or follow-up (severity scores).

Clinical Dehydration Scales

It would be helpful to have a common tool to evaluate dehydration. The use of the Clinical Dehydration Scale (CDS) is supported by consistent evidence, and it is easy to use in the assessment of dehydration (III, C) (weak recommendation, low-quality evidence).

This scale should be used in combination with other criteria to guide the need of medical interventions in individual cases (III, C) (weak recommendation, low-quality evidence).

TABLE 3. CDS for children (total score from 0 to 8)

Characteristics	0	1	2
General appearance	Normal	Thirsty, restless or lethargic but irritable when touched	Drowsy, limp, cold or sweaty ± comatose
Eyes	Normal	Slightly sunken	Extremely sunken
Mucous membranes (tongue)	Moist	Sticky	Dry
Tears	Tears	Decreased tears	Absent tears

A score of 0 represents no dehydration; a score of 1 to 4, some dehydration; and a score of 5 to 8 moderate/severe dehydration. CDS = clinical dehydration scale.

In 2008 the ESPGHAN/ESPID Working Group observed that none of the dehydration scales available at that time had been validated in individual patients. Therefore, they concluded that there was insufficient evidence to support the use of any 1 single scoring system for the management of the individual child.

Starting in 2008, a number of studies were conducted to validate the CDS for children 1 to 36 months with AGE in the emergency department (ED) (81). The scale was developed using formal measurement methodology, namely, item selection and reduction, reliability, discriminatory power, validity, and responsiveness. It consists of 4 clinical items: general appearance, eyes, mucous membranes, and tears. Each item is rated from 0 to 2, and the total score ranges between 0 and 8. The final 3 categories were as follows: no dehydration (CDS score: 0), some dehydration (CDS score: 1–4), and moderate/severe dehydration (CDS score: 5–8) (Table 3).

The CDS was validated in several clinical studies. It was found to be useful in predicting the need for intravenous (IV) rehydration (82,83), weight gain (83), need for blood test (83,84), need for hospitalization (83), and the length of stay in hospital and in the ED (82,84). CDS was characterized by moderate-to-good interobserver reliability (83,85).

Roland et al (86) proposed a standardized scoring system that consists of 7 clinical items: mucous membranes, skin turgor, sunken eyes, respiratory rate, pulse rate, neurological status, and capillary refill time, each scored 0–2, which is summed for a total score ranging between 0 and 10. The study, which involved 100 children with symptoms of gastroenteritis, showed that a standardized scoring system of clinical signs did not reduce the variability between physicians' assessments of the dehydrated children.

Other methods of estimating dehydration status that may require specific tools have been evaluated, namely, the use of ultrasound to measure the inferior vena cava (IVC) diameter (87), the ratio of IVC to aorta diameter (88), the aorta to IVC ratio and IVC inspiratory collapse (89), bedside hand-held bladder ultrasound scanning (90), and digital videography to measure capillary refill time (91), or bioelectric impedance (92). Although some of these methods are promising, further studies are required to validate these diagnostic tools in the assessment of dehydration in children.

Severity Scores

Severity scores provide a more global measure of general clinical involvement and include dehydration and other parameters. Limited but solid evidence support their use. The classic Vesikari scale is a 20-point score (93) and a more simple score consists of 7 variables to differentiate whose scores range between 0–8, 9–10, and ≥11, which correspond to mild, moderate, and severe illness, respectively. Recently, Schnadower et al (94) demonstrated that this score significantly correlates with the grade of dehydration, hospitalization, and subsequent day care and work absenteeism. The authors concluded that this score is a reliable tool for the assessment of the global severity of gastroenteritis and supported its use in multisite outpatient clinical trials (Table 4).

6.3 Is There Any 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 involvement each suggests a bacterial pathogen. Vomiting and respiratory symptoms are associated with a viral etiology (III, C) (weak recommendation, low-quality evidence).

No clinical feature of AGE can differentiate a bacterial from a viral etiology. Children with viral intestinal infection had significantly more respiratory symptoms and presented with more frequent and longer-lasting vomiting than children with bacterial intestinal infection (25). Two observational studies of European children <5 years, one involving 680 Italian outpatients (60) and the

TABLE 4. Modified Vesikari score

Points	0	1	2	3
Diarrhea duration, h	0	1–96	97–120	≥121
Maximum number of diarrheal stools per 24-h period (in the course of the disease)	0	1–3	4–5	≥6
Vomiting duration, h	0	1–24	25–48	≥49
Maximum number of episodes per 24-h period (in the course of the disease)	0	1	2–4	≥5
Maximum recorded fever, °C	<37.0	37.1–38.4	38.5–38.9	≥39.0
Future health care visit	0	—	Primary care	Emergency department
Treatment	None	IV rehydration	Hospitalization	—

Adapted from (94). IV = intravenous.

other involving 4880 German inpatients (46), found that rotavirus-positive AGE is more likely to be associated with fever, dehydration, and electrolyte imbalance than rotavirus-negative episodes. Compared with other viral infections, rotavirus infection is associated with high-grade fever (>38°C), more frequent diarrheal episodes (>7/day), and longer-lasting diarrhea, and, consequently, it results in significantly higher severity scores (25,59,95). In contrast, children with norovirus infection have significantly more episodes of vomiting than children with other viral infections, and in some cases, vomiting may be the only gastrointestinal symptom (up to 20% of patients present without diarrhea) (25,95).

A pattern of ''colitis'' characterized by numerous diarrheal episodes with small amounts of stool (25,96), bloody stools, high fever, and abdominal pain (96) is more likely to be associated to bacterial enteric infections.

7. DIAGNOSTIC WORKUP

Acute gastroenteritis does not generally require a specific diagnostic workup (Vb, D) (strong recommendation, low-quality evidence).

7.1 Are Microbiological Investigations Useful in Children With AGE?

Children presenting with AGE do not require routine etiological investigation; however, there may be particular circumstances in which microbiological investigations may be necessary for diagnosis and treatment (Vb, D) (strong recommendation, low-quality evidence).

Microbiological investigations may be considered in children with underlying chronic conditions (eg, oncologic diseases, IBDs, etc), in those in extremely severe conditions, or in those with prolonged symptoms in whom specific treatment is considered. (Vb, D) (strong recommendation, very low-quality evidence).

Microbiological investigation is not helpful in most cases. Stools should be sampled during outbreaks, especially in childcare, school, hospital, and residential settings, where there may be a public health need to identify the pathogen and establish its source. Children with severe bloody diarrhea or a history of travel to at-risk areas may benefit from etiology investigation.

7.2 Is There Any Reliable Hematological Marker of Bacterial Diarrhea?

The differentiation of a bacterial from nonbacterial etiology is not likely to change treatment. C-reactive protein (CRP) and procalcitonin measurements are not routinely recommended to identify a bacterial etiology (Vb, D) (weak recommendation, low-quality evidence).

There is a lack of good-quality studies of the effectiveness (reliability) and ability of specific laboratory tests to distinguish between bacterial and viral gastroenteritis (25).

Evidence suggests that raised CRP, also measured with the Quick Read-CRP test (97), can detect bacterial causes of AGE, although poor evidence quality should be taken into consideration. Normal CRP does not exclude the possibility of bacterial gastroenteritis. Other acute-phase proteins (interleukin [IL]-6, IL-8, and IL-10), and raised erythrocyte sedimentation rate levels were found to be less accurate than CRP. Procalcitonin seems to be more effective than CRP in differentiating between viral and bacterial AGE (98), but additional data are needed before its use can be recommended.

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

Based on available data we do not recommend the routine use of fecal markers to distinguish between viral and bacterial AGE in the clinical setting (Vb, D) (weak recommendation, low-quality evidence).

Compared with fecal lactoferrin, fecal calprotectin more closely reflects intestinal inflammation. This in turn is more frequently associated with a bacterial than with a viral or parasitic etiology.

Both fecal markers (calprotectin and lactoferrin) have been studied mostly in relation to the diagnosis and monitoring of IBD. Although they are good indicators of IBD, neither is specific for the disease. In fact, elevated levels have been found in other diseases of the gastrointestinal tract, namely, infectious gastroenteritis, cancer, polyposis, allergy, celiac disease, cystic fibrosis, protein-losing enteropathy, necrotizing enterocolitis, immunodeficiency, and diverticular disease (99).

The evaluation of fecal calprotectin combined with CRP showed a diagnostic accuracy of 94% for bacterial AGE (100).

Fecal lactoferrin is higher in patients with *Salmonella* or *Campylobacter* infection than in patients with viral infection (101), and is significantly correlated with disease severity measured with the Vesikari and Clark scores.

7.4 Does Any Biochemical Test Change the Approach to the Child With AGE?

Tests of dehydration are imprecise, and, generally, there is only fair-to-moderate agreement with the examiner's estimate (III, C) (weak recommendation, low-quality evidence).

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

Electrolytes should be measured in hospital settings:

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

Several studies tried to define key clinical and laboratory markers that can be used to objectively measure the degree of dehydration. On the contrary, laboratory studies, including serum electrolytes, are generally unnecessary in cases of AGE with mild-to-moderate dehydration. Laboratory tests may be considered in dehydrated children if IV rehydration therapy is started, if there are signs and symptoms of hypernatremia, and in case of shock. Serum bicarbonate, blood urea nitrogen, and low pH combined with a high base excess correlate best with the percentage of weight loss; however, none of the laboratory tests studied so far can accurately estimate the percentage of weight loss in a general pediatric practice.

Serum sodium, potassium, creatinine, blood urea, and glucose and the level of dehydration were assessed in 251 children admitted to hospital with AGE (102). In this study, which suffers from severe methodological limitations, serum urea was the best among all parameters in predicting levels of dehydration. The results of this study are in disagreement with the recommendations on laboratory testing in AGE set out in the American Academy of Pediatrics Practice Parameters (77) and in the previous ESPGHAN/ESPID guidelines. Owing to the methodological limitations of the above-mentioned study, there is insufficient evidence to change present recommendations for biochemical testing in children with AGE.

In summary, there are no data to support the presence and utility of clinically significant biochemical disturbances in children with gastroenteritis. High plasma bicarbonate levels were significantly associated with the absence of dehydration, but the practical usefulness of bicarbonate estimation in the detection of dehydration is unclear.

7.5 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 such as differential diagnosis with IBD at its onset (Vb, D) (strong recommendation, low-quality evidence).

No studies have appeared since the 2008 guidelines. Endoscopy, however, may be useful in the diagnosis of the infectious agent in hospitalized or at-risk children presenting with chronic diarrhea. Such agents as *C difficile* are associated with a typical endoscopic pattern of, for example, pseudomembranous colitis (103,104).

8. HOSPITAL MANAGEMENT

Gastroenteritis is a major cause of hospital admission and has a major impact on costs (105). Recently, an increase in emergency admission to hospital has been observed in the United Kingdom (106). The hospitalization rate in the United Kingdom in 2011 was 65.7/10,000 children <5 years (74), although implementation of guidelines reduced IV rehydration (107). Hospital practice varies greatly among institutions in developed communities, and many children who are not severely dehydrated are admitted to hospital and receive unnecessary interventions; therefore, there is a need for standardized management (108,109).

8.1 What Are the Indications for Hospitalization?

The recommendations for hospital admission are based on consensus and include any of the following conditions (Vb, D) (strong recommendation, low-quality evidence):

- Shock
- Severe dehydration (>9% of body weight)
- Neurological abnormalities (lethargy, seizures, etc)
- Intractable or bilious vomiting
- Failure of oral rehydration
- Suspected surgical condition
- Conditions for a safe follow-up and home management are not met

There are no established admission criteria for AGE. Case-controlled studies cannot be performed for ethical reasons.

Social and logistical concerns are still a questionable indication for hospital admission for AGE (74,75).

8.2 What Hygiene and Isolation Precautions Are Indicated for a Child With AGE?

Contact precautions are advised in addition to standard precautions (hand hygiene, personal protective equipment, soiled patient-care equipment, environmental control including textiles, laundry and adequate patient placement) (Vb, D) (strong recommendation, very low-quality evidence).

As indicated by the American Academy of Pediatrics (110) the following contact precautions are indicated during management of children with AGE:

- If possible, single-patient room (for younger children who do not control body excretions)
- Gloves (nonsterile)
- Hand hygiene after removal of gloves
- Gowns should be worn during procedures and patient-care activities

Cohorting is discouraged, even if based on etiology, because of the risk of harboring multiple agents that may worsen the disease (29).

8.3 What Are the Indications for Nasogastric Rehydration?

When oral rehydration is not feasible, enteral rehydration by the nasogastric (NG) route is the preferred method of rehydration, and should be proposed before IV rehydration (I, A) (strong recommendation, moderate-quality evidence).

Enteral rehydration is associated with significantly fewer major adverse events and a shorter hospital stay than IV rehydration and is successful in most children (I, A) (strong recommendation, moderate-quality evidence).

The rapid (40–50 mL/kg within 3–6 hours) and standard (24 hours) NG rehydration regimens are equally effective and may be recommended (II, B) (weak recommendation, moderate-quality evidence).

Health care providers and caregivers are more familiar with IV than with NG rehydration (111). A shift from the former to the

latter practice requires changes in management strategies, and there is no proof of success.

There is no agreement about the amount of fluids that should be administered through an NG tube. Data on NG rehydration regimens may be extrapolated from studies included in meta-analyses (112) and from 2 systematic reviews (113). The regimens were similar in all trials, and a total volume of 40 to 50 mL/kg for 3 to 6 hours was usually administered.

A randomized, controlled trial (RCT) conducted in Australia, which was the only 1 to specifically compare 2 different NG regimens in children accessing emergency, did not find any differences in terms of efficacy and safety between standard (>24 hours) and rapid (4 hours) replacement of fluid losses (114); however, although the authors concluded that rapid NG tube rehydration may reduce the need for hospitalization, about one-quarter of rapidly rehydrated patients needed additional fluids and failed to be discharged.

8.4 What Are the Indications for IV Rehydration?

IV fluids are required in the following cases (Vb, D) (strong recommendation, low-quality evidence):

- Shock
- Dehydration with altered level of consciousness or severe acidosis
- Worsening of dehydration or lack of improvement despite oral or enteral rehydration therapy
- Persistent vomiting despite appropriate fluid administration orally or via an NG tube
- Severe abdominal distension and ileus

Oral rehydration is the first-line treatment for all of the children with AGE, and an efficacy comparable with IV has been reported also in children with severe dehydration (115,116). Selected clinical conditions may, however, require IV rehydration. The following recommendations derive from expert consensus opinion and are similar to recommendations in other guidelines (79,117,118).

Because oral rehydration is more effective and less invasive than IV rehydration, administration of ORS should be attempted and promoted. In the case of children on IV therapy, attempts should be made to switch to oral rehydration as soon as indications for parenteral rehydration are no longer observed.

8.5 How to Administer IV Fluids

For Children Presenting With Shock

Children presenting with shock secondary to AGE should receive rapid IV infusion of isotonic crystalloid solution (0.9% saline or lactated Ringer's solution) with a 20-mL/kg bolus (Vb, D) (strong recommendation, very low-quality evidence).

If the blood pressure has not improved after the first bolus, a second (or even a third) bolus of 20 mL/kg should be administered >10 to 15 minutes and other possible causes of shock should be considered (Vb, D) (strong recommendation, very low-quality evidence).

For Children With Severe Dehydration Without Shock

Children with severe dehydration requiring IV fluids may receive rapid rehydration with 20 $mL \cdot kg^{-1} \cdot h^{-1}$ of 0.9% saline solution for 2 to 4 hours (II, B) (strong recommendation, moderate-quality evidence).

In IV-rehydrated children, a dextrose-containing solution may be used for maintenance (III, C) (weak recommendation, low-quality evidence).

A solution containing not <0.45% saline (at least 77 mEq/L [Na^+]) is recommended during the first 24 hours of IV rehydration therapy to prevent hyponatremia (III, C) (weak recommendation, low-quality evidence).

After the child starts to urinate and if serum electrolyte values are known, add 20 mEq/L of K^+ chloride (Vb, D) (weak recommendation, low-quality evidence).

The modality for IV fluid therapy in children has been poorly studied, and a standardized protocol based on strong evidence of efficacy is not available. Most reported schemes vary in terms of volumes, duration, and fluid composition, and, in most cases, are supported only by historic recommendations and personal clinical experience.

8.5.1 IV Rehydration Rates

Rapid rehydration with 20 $mL \cdot kg^{-1} \cdot h^{-1}$ for 2 to 4 hours followed by oral rehydration or continuous infusion of dextrose solution is adequate for initial rehydration of most patients requiring hospital assistance (II, B) (strong recommendation, moderate-quality evidence).

More rapid IV rehydration may be associated with electrolyte abnormalities and is associated with long time to hospital discharge, and therefore is not recommended (II, B) (strong recommendation, low-quality evidence).

Rehydration therapy with IV fluids has traditionally been administered slowly, typically for 24 hours (119). Consequently, it took a long time to rehydrate children and they remained in hospital for a prolonged period. The aim of IV rehydration is to replace the loss of fluids due to AGE and ongoing physiological fluid losses (maintenance), which is calculated according to the Holliday–Segar scheme (120) (Table 5).

Many experts now favor more rapid IV rehydration. In fact, rapid replacement of extracellular fluids, which improves gastrointestinal and renal perfusion, allows earlier oral feeding and a faster correction of electrolyte and acid–base abnormalities, which, in turn, results in an excellent recovery rate and shorter duration of hospitalization (121,122). The WHO recommends IV rehydration be completed within 3 to 6 hours depending on age (123).

TABLE 5. Holliday–Segar method to calculate maintenance fluid

Child's weight	Baseline daily fluid requirement
1–10 kg	100 Ml/kg
10–20 kg	1000 Ml + 50 Ml/kg for each kg >10 kg
>20 kg	1500 Ml + 20 Ml/kg for each kg >20 kg

Given this scenario, various scientific societies recommend a rapid IV infusion of approximately 20 $mL \cdot kg^{-1} \cdot h^{-1}$ 0.9% saline for 2 to 4 hours followed by oral rehydration treatment or a continuous infusion of dextrose-containing crystalloid solution, if prolonged IV hydration is required (77,117,124).

A prospective study that compared a new rapid scheme (20 $mL \cdot kg^{-1} \cdot h^{-1}$ 0.45% saline in 2.5% dextrose) with a historic 24-hour rehydration scheme demonstrated a significant reduction in admission rate and length of ED stay in moderately dehydrated children (125). Even faster rehydration schemes are gradually being used in clinical practice with the aim of obtaining faster control of symptoms, shorter hospital/ED stays, and a reduction of the global costs of AGE. In an RCT that compared 2 rapid IV schemes, tolerance to the administration of 50 mL/kg in 1 hour was similar to that of 50 mL/kg in 3 hours, but it was associated with earlier discharge from ED (2 vs 4 hours) (126).

A blinded RCT of children accessing the ED compared the efficacy of 20 mL/kg (standard regimen) and 60 mL/kg (standard regimen) of 0.9% saline infusion for 1 hour, followed by 5% dextrose in 0.9% saline for maintenance (127). No difference was observed between the 2 groups in terms of percentage of children rehydrated after 2 hours, treatment duration, dehydration scores, readmission to emergency, or adequate oral intake. In the same children, those randomized to ultrarapid IV rehydration (60 mL/kg) experienced a greater mean increase in serum sodium and were less likely to have a serum sodium decrease $\geq$2 mEq/L than children receiving standard rate infusion (128); however, the median time-to-discharge was slightly longer in the ultrarapid than in the standard group, and more children receiving rapid IV rehydration were admitted to hospital.

These data and the trend toward worse outcomes in children with AGE do not support the use of ultrarapid IV rehydration schemes, and caution should be exercised before recommending the routine use of such a scheme.

8.5.2 Composition of Fluids for Rehydration

Isotonic (0.9%) saline solution effectively reduces the risk of hyponatremia and is recommended for initial rehydration in most cases. In the rare but extremely severe cases of shock, Ringer's lactate solution is recommended (III, C) (strong recommendation, low-quality evidence).

Glucose may be added to saline solution once fluid volume has been restored in the subsequent phase of IV rehydration (''maintenance'') (III, C) (weak recommendation, low-quality evidence).

There is no standard fluid composition for IV rehydration regimens in children with AGE. UK and US guidelines recommend the use of isotonic fluids (0.9% saline or lactated Ringer's solution) to start IV rehydration to reduce the risk of hyponatremia (79,117), and in a survey of pediatricians working in EDs in Canada and the United Sates, 93% of responders prescribed normal saline for IV rehydration (129).

A meta-analysis of 6 trials of the effects of IV rehydration in children with different illnesses showed that the administration of hypotonic solutions significantly increased the risk of developing acute hyponatremia and was associated with increased morbidity and lower values of serum sodium after treatment (130); however, only 1 RCT specifically included children with AGE (131). It found that Na^+ blood concentration was significantly better in children receiving standard isotonic solution than in those receiving the hypotonic solution. A subsequent retrospective study on children receiving hypotonic IV solutions found that 19% of children isonatremic at admission developed mild hyponatremia during treatment (132).

Once IV fluids have restored the fluid volume, children can be shifted to a dextrose-containing solution. Glucose added to maintenance solutions may support brain metabolism and reduce body protein catabolism and sodium loss (133). A case–control study on preschool children with AGE demonstrated that children who received smaller amounts of dextrose-containing IV solution to correct dehydration were significantly more likely to return to hospital and be admitted, irrespective of the amount of fluid administered (134).

8.5.3 Treatment of Hypernatremia

Oral or NG rehydration with hypoosmolar ORS is an effective and safe treatment and has fewer adverse effects than IV rehydration (III, C) (weak recommendation, very low-quality evidence).

If the child is hypernatremic and needs IV rehydration:

- Use an isotonic solution (0.9% saline) for fluid deficit replacement and maintenance (III, C) (strong recommendation, very low-quality evidence).
- Replace the fluid deficit slowly, typically for 48 hours, with the aim of reducing it to <0.5 $mmol \cdot L^{-1} \cdot h^{-1}$ (III, C) (weak recommendation, very low-quality evidence).
- Monitor plasma sodium frequently (Vb, D) (weak recommendation, very low-quality evidence).

Hypernatremic dehydration ($Na^+ > 145$ mmol/L) is rare during AGE; its frequency varies between $<1\%$ to 4% of cases depending on setting and definition (135–137). In children with hypernatremia, dehydration may be underestimated owing to the lack of typical clinical signs; children (mainly infants <6 months) may present with ''doughy'' skin, tachypnea, and neurological signs, namely increased muscle tone, hyperreflexia, convulsions, drowsiness, or coma.

The route of fluid administration does not seem to affect the risk of hypernatremia acquired during rehydration therapy. In a Cochrane review that compared the effects of enteral and IV rehydration, the incidence of hypernatremia did not differ statistically between the 2 types of rehydration (112). An early trial that compared enteral rehydration with ORS versus IV rehydration with Ringer's solution reported a higher rate of seizures (25% vs 6%) in children undergoing IV rehydration (116).

Two retrospective studies demonstrated the safety of IV rehydration in children with hypernatremic dehydration. The first study reported good outcomes in children treated with maintenance fluid plus 50 (moderately dehydrated) or 100 (severely dehydrated) mL/kg IV solution containing approximately 60 mmol/L Na (Na^+ blood level should not be reduced faster than 0.6 $mmol \cdot L^{-1} \cdot h^{-1}$ (138) A more recent retrospective study confirmed the efficacy of normal 0.9% saline given as bolus followed by a 48-hour infusion of 0.9% saline in 5% dextrose for treatment of diarrhea-related hypernatremia (139).

8.6 Can Any Therapeutic Intervention Reduce the Length of Hospital Stay?

Administration of effective probiotic strains reduce the duration of hospital stay and may be considered in children admitted with AGE (II, B) (strong recommendation, low-quality evidence).

Hospitalized children with severe rotavirus gastroenteritis may benefit from oral administration of serum immunoglobulins (III, C) (weak recommendation, very low-quality evidence).

Lactose-free formulas can be considered in the management of AGE in hospitalized children age <5 years (I, A) (weak recommendation, low-quality evidence).

Once a child with AGE has been admitted, the time spent in the hospital depends on the underlying clinical condition, and essentially the duration of diarrhea, vomiting, and the ability to tolerate oral rehydration. The simple replacement of lost fluids does not shorten the course of diarrhea, but interventions to reduce the duration of symptoms may be applied.

Probiotics

Several probiotic strains have been tested in hospitalized children with different results. Despite consistent evidence that probiotics reduce the duration of diarrhea, there is only weak evidence for their efficacy in reducing the duration of hospitalization.

A review reported that administration of probiotics in hospitalized children reduced the mean length of hospitalization by 1.12 days (95% confidence interval [CI] −1.16 to 0.38) (140). Compelling evidence in support of effective strains is available for *Lactobacillus rhamnosus* GG and *S boulardii*. A subgroup analysis of 4 RCTs (n = 1615) showed a reduction in the duration hospitalization for children treated with *Lactobacillus* GG (LGG) compared with the control group (mean difference [MD] = 0.82 day, 95% CI 0.95 to −0.69). This result was, however, not confirmed in a random-effects model (MD = 1.42 days, 95% CI 3.05–0.21) (141), probably because of a borderline difference in the duration of diarrhea between treated and control children (n = 1768, MD 0.61 day, 95% CI 1.4–0.19).

Few trials have examined the effect of *S boulardii* on hospitalization. A review reported that administration of this probiotic strain may reduce the duration of hospitalization in inpatient children (n = 449, MD = −0.8 day, 95% CI −1.1 to −0.5) (142). Although data on hospital stay are not conclusive, the use of probiotics in this setting may have significant impact on the health care burden of AGE and diarrhea-associated costs.

Nutritional Interventions

A Cochrane review (143) evaluated the efficacy of lactose-free vs lactose-containing diets in children age <5 years. The review (33 trials, 2973 children) included 29 studies conducted exclusively on inpatients, all from high- or middle-income countries. Compared with lactose-containing milk, milk products, or foodstuffs, lactose-free products were associated with a reduction of diarrhea in hospitalized children by approximately 18 hours (MD −17.94, 95% CI −26.28 to −9.59, 14 trials, 1342 participants). Treatment failure was defined in various ways (continued or worsening diarrhea or vomiting, the need for additional rehydration therapy, or continuing weight loss and lactose-free products reduced treatment failure with a relative risk of 0.52 (95% CI 0.39–0.68, 18 trials, 1470 participants). Data were, however, different in outpatients setting.

Other Treatments

Oral administration of immunoglobulins in rotaviral AGE reduced the length of stay in severe and/or immunocompromised patients and in patients with severe diarrheal episodes (see Antiviral Treatment).

Other drugs such as smectite (144,145) and racecadotril (146) have proven effective in reducing the duration of symptoms in children with AGE (see Pharmacological Therapy).

A recent article comparing the efficacy of a product containing smectite and LGG versus LGG alone in children hospitalized for AGE demonstrated a significantly shorter duration of IV therapy but did not find any effect on duration of hospitalization (147).

A deterministic and probabilistic sensitivity analysis on the economic impact of racecadotril showed a reduction in hospital costs related to an AGE event of approximately £380 compared with ORS. The amount spared is related to primary care reconsultation and, mainly, to secondary care costs (148).

8.7 When to Discharge a Child Admitted Because of Acute Gastroenteritis

Prompt discharge from hospital should be considered in children admitted for AGE when the following conditions are fulfilled (Vb, D) (weak recommendation, low-quality evidence):

- Sufficient rehydration is achieved as indicated by weight gain and/or clinical status
- IV fluids are no longer required
- Oral intake equals or exceeds losses
- Medical follow-up is available via telephone or office visit

A child may be discharged from hospital when he or she no longer needs therapeutic or diagnostic procedures that must be performed in a hospital setting and when the family is able to safely manage him or her at home. In most cases, this does not correspond with complete recovery from AGE and complete cessation of diarrhea. It is important to distinguish between discharge from hospital and the child's return to a normal social life; the latter may require some extra days after discharge when the stools become more formed and the child has a better control and a frequency of evacuations. An early hospital discharge may result in readmission to the ED; however, in a recent retrospective analysis of 40,000 children with acute illnesses discharged from the ED on the same day as admission, AGE was not related to a higher risk of readmission (149). Providing effective information may improve caregivers' ability to manage their child at home and hence reduce the possibility of readmission to hospital. A recent nonrandomized educational trial demonstrated that verbal reinforcement of written discharge instructions by a discharge facilitator improves parental recall of discharge instructions for AGE (150).

9. TREATMENT

9.1 Rehydration

9.1.1 Reduced Osmolarity ORS

Reduced osmolarity ORS (50/60 mmol/L Na) should be used as first-line therapy for the management of children with AGE (I, A) (strong recommendation, moderate-quality evidence).

Reduced osmolarity ORS is more effective than full-strength ORS as measured by such important clinical outcomes as reduced stool output, reduced vomiting, and reduced need for supplemental IV therapy (I, A) (strong recommendation, moderate-quality evidence).

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) (strong recommendation, moderate-quality evidence).

Modified ORS

There is insufficient evidence to recommend in favor or against the universal addition of enriched ORS (II, B) (weak recommendation, low-quality evidence).

Efforts to improve the efficacy of ORS continue. These include the addition to ORS of zinc (151), zinc and prebiotics (fructooligosaccharides and xylooligosaccharides) (152), glucose polymers (153) (154), L-isoleucine (155), or honey (156). Although some interventions are promising, no major breakthrough has been made since the discovery of the scientific basis for oral rehydration and the introduction of ORS into daily practice. Furthermore, most studies were carried out in low-income countries, which limits their relevance to the European population.

There is limited evidence for similar efficacy of ORS with standard taste and ORS with improved taste (II, B) (weak recommendation, moderate-quality evidence).

Frozen fruit-flavored ORS is better tolerated than conventional ORS (III, C) (weak recommendation; very low-quality evidence).

Three RCTs investigated ORS with improved taste. Two were conducted on healthy children (157,158) to test acceptance. One RCT that compared an apple-flavored hypotonic ORS with a regular hypotonic ORS in outpatients showed that they were equally effective and may be used interchangeably (159).

One controlled, crossover trial compared standard ORS with flavored frozen solution. Children were more likely to tolerate the frozen solution than the conventional solution ($P < 0.001$). For treatment failures, after crossover, a significantly higher percentage of children tolerated the full amount of the frozen solution than the reverse (160).

9.2 Nutritional Management

Both the ESPGHAN/ESPID guidelines and the National Institute for Health and Care Excellence guidelines agree on the key recommendations related to the diagnosis and management of AGE, including fast oral rehydration with rapid reintroduction of previous regular feeding. All guidelines state that breast-feeding should be continued throughout rehydration, an age-appropriate diet should be started during or after initial rehydration (4–6 hours), and dilution of the formula or the use of a modified milk formula is usually unnecessary.

9.2.1 Early Versus Late Feeding of a Child With AGE

Early resumption of feeding after rehydration therapy is recommended. Further studies are, however, needed to determine whether the timing of refeeding affects the duration of diarrhea, total stool output, or weight gain in childhood acute diarrhea (I, A) (strong recommendation, low-quality evidence).

Early refeeding has been advocated to enhance enterocyte regeneration, promote recovery of brush-border disaccharidases, nutrient absorption, and weight gain. Early studies showed that early refeeding has a significant nutritional advantage, especially in malnourished children.

A recent Cochrane review analyzed the data on early (food intake during or immediately after rehydration onset) versus late refeeding (food intake 20 to 48 hours after rehydration onset) in children age <10 years with acute diarrhea. The review included 12 trials (1226 participants) published between 1979 and 1997. Only 2 trials considered the participants' nutritional status. The type of feeding included breast milk, or cow's-milk formula (full-strength or half-strength), or soy- or rice-based formula. There was no significant difference between early and late refeeding groups in the number of participants who needed unscheduled IV fluids (6 trials with 813 participants), who experienced episodes of vomiting (5 trials with 466 participants), and who developed persistent diarrhea (4 trials with 522 participants). The mean length of hospital stay was also similar in the 2 groups (2 trials with 246 participants). Overall, diarrhea lasted longer in the late refeeding group than in the early refeeding group, although the MD was not significant. The comparison of the mean total stool volume in the first 24 and 48 hours (3 trials) after starting rehydration showed significant heterogeneity and no conclusion could be drawn. No difference was observed in the mean percentage weight gain at the 24th hour after starting rehydration or at resolution of illness (4 trials). No adverse effects were associated with the practice of early refeeding, as reported in the Cochrane meta-analysis. Most studies were, however, conducted >20 years ago, and some important outcomes could not be assessed because of methodological diversity (161).

9.2.2 Are Modified Formulas Indicated for AGE?

The routine use of lactose-free feeds is presently not recommended in outpatient setting (I, A) (strong recommendation, low-quality evidence).

There is insufficient evidence to recommend in favor or against the use of diluted lactose-containing milk (I, A) (weak recommendation, low-quality evidence).

There is some evidence that lactose-free feeds can decrease the duration of diarrhea compared with lactose-containing feeds, but the evidence is limited in outpatients. As reported above (see section Can Any Therapeutic Intervention Reduce the Length of Hospital Stay?), a recent Cochrane review (143) demonstrated a shorter duration of diarrhea in hospitalized children receiving lactose-free products compared with lactose-containing milk. The only 2 studies including outpatient children (143 participants), however, did not find any significant effect of lactose-free formulas on diarrheal duration (7.59 hours 95% CI −83.51 to 98.69).

Diluted lactose-containing milk did not reduce diarrhea duration compared with undiluted milk or milk products (5 trials, 417 participants), but showed a potential for reducing the risk of prolonged or worsening diarrhea (relative risk 0.65, 95% CI 0.45–0.94, 9 trials, 687 participants).

9.2.3 Milk-Free Mixed Diets, Cereal-Based Milk/Formulas, Home Available Staple Foods, and Other Types of Food or Drinks

The bread, rice, apple, toast (BRAT) diet has not been studied and is not recommended (Vb, D) (strong recommendation, low-quality evidence).

Beverages with a high sugar content should not be used (III, C) (strong recommendation, low-quality evidence).

There is a lack of new good-quality evidence to support a change of the present recommendations with regard to nutritional management during AGE in children in Europe.

An RCT, published after the 2008 guidelines, performed in Bangladesh in children undergoing standard antibiotic treatment for *Shigella*, compared a rice-based diet supplemented with green bananas versus rice-based diet without green bananas. Bloody diarrhea was reduced in the green banana group (96% vs 60%) (162).

9.3 Pharmacological Therapy

9.3.1 Antiemetics

Ondansetron

Ondansetron, at the dosages used in the available studies and administered orally or intravenously, may be effective in young children with vomiting related to AGE. Before a final recommendation is made, a clearance on safety in children is, however, needed (II, B) (strong recommendation, low-quality evidence).

The authors of a meta-analysis (163) of 6 RCTs found that ondansetron therapy decreased the risk of persistent vomiting, reduced the need for IV fluids, and decreased the risk of immediate hospital admission in children with vomiting as a result of gastroenteritis; however, compared with placebo, ondansetron significantly increased stool outputs in treated patients, and it did not affect return to care.

A more recent Cochrane review (164) included 7 RCTs that compared ondansetron therapy with placebo and 4 of these investigated oral route of administration. Children age <18 years who presented with vomiting and had a clinical diagnosis of gastroenteritis were enrolled. Compared with placebo, ondansetron significantly increased the proportion of children with cessation of vomiting, and reduced the need for IV therapy and the immediate hospital admission rate. In 3 RCTs, there was a significantly increased rate of stool outputs in the ondansetron group ($P < 0.05$). A critical overview of data available in the Cochrane database of systematic reviews showed that children who received oral ondansetron had lower hospital admission rates to ED compared with placebo and lower risk of receiving IV rehydration (140).

Only the Canadian Pediatric Society (165) has recommended that oral ondansetron therapy, as a single dose, be considered for children from 6 months to 12 years of age with vomiting related to suspected AGE, and who have mild-to-moderate dehydration or who have failed oral rehydration therapy. The use of ondansetron was not recommended in children with AGE predominantly presenting as moderate-to-severe diarrhea because one of the most common adverse effects of ondansetron is increased frequency of diarrhea. Of note, although outside the context of diarrhea, in a ''black box'' alert issued in September 2011, the Federal Drug Agency recommended electrocardiogram monitoring in patients with ''electrolyte abnormalities (eg, hypokalemia or hypomagnesemia)'' who are receiving ondansetron because they may be at risk for developing prolongation of the QT interval, which can lead to an abnormal and potentially fatal heart rhythm, including *Torsade de Pointes* (166).

Other Antiemetics

There is no evidence to support the use of other antiemetics (II, B) (strong recommendation, low-quality evidence).

The effects of the antiemetics dexamethasone, dimenhydrinate, granisetron, and metoclopramide have also been studied using a meta-analytic approach (163,164). These analyses indicate that there is no evidence to support the use of dexamethasone or metoclopramide, and there is only limited evidence that granisetron or dimenhydrinate stops vomiting. A double-blind RCT, published after the above meta-analyses, confirmed that compared with placebo, oral dimenhydrinate did not affect the frequency of vomiting in children 1 to 12 years of age with AGE (167).

The protocol of a new multicenter RCT comparing oral ondansetron versus domperidone for symptomatic treatment of vomiting during AGE in children has been published (168). A multicenter RCT conducted in 56 Japanese children with AGE, however, failed to show the efficacy of domperidone with ORS compared with ORS alone in reducing early vomiting in AGE (169). A warning about possible cardiac effects by domperidone was released in March 2014 by the European Medicines Agency, with specific reference to its use in children with vomiting (*http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/03/WC500162558.pdf*).

9.3.2 Antimotility or Antiperistaltic Drugs (Loperamide)

Loperamide is not recommended in the management of AGE in children (II, B) (strong recommendation, very low-quality evidence).

No new RCTs were identified.

9.3.3 Adsorbents

Diosmectite

Diosmectite can be considered in the management of AGE (II, B) (weak recommendation, moderate-quality evidence).

Two RCTs have been published since the previous guidelines; however, neither was performed in a high-income country. Dupont et al (144) carried out 2 parallel, double-blind studies to

evaluate the efficacy of diosmectite on stool reduction in 602 children with acute watery diarrhea from 2 countries (Peru and Malaysia). The results are reported separately for the 2 populations because of differences in the definitions of some outcomes. In Peru (n = 300), the 72-hour cumulative stool output was lower ($P = 0.032$) and diarrhea duration shorter ($P = 0.001$) in the diosmectite group than in the placebo group. The positive effect of diosmectite was confirmed in both rotavirus-positive and rotavirus-negative children. In Malaysia (n = 302), the 72-hour stool output was also significantly lower in children who received diosmectite than in controls ($P = 0.007$). The median duration of diarrhea was significantly shorter in children who received diosmectite than in controls ($P = 0.001$); however, the beneficial effect was observed in rotavirus-negative children only.

A more recent open RCT carried out in India also found that diosmectite reduced the duration of diarrhea and prevented a prolonged course (145). The time for resolution of the diarrhea was significantly shorter ($P < 0.001$) as was the total duration of diarrhea ($P < 0.001$) in the diosmectite group than in the control group.

Diosmectite Plus LGG

> Smectite plus LGG and LGG alone are equally effective in the treatment of young children with AGE. Combined use of the 2 interventions is not justified (II, B) (weak recommendation, low-quality evidence).

In countries where both LGG and smectite are available, their concomitant use is frequently practiced. One double-blind placebo-controlled RCT compared LGG plus smectite with LGG alone (147). The duration of diarrhea was similar ($P = 0.43$) in the LGG/smectite (n = 44) and LGG/placebo groups (n = 37).

Other Absorbents

> Other absorbents (namely, kaolin–pectin and attapulgite-activated charcoal) are not recommended (III, C) (weak recommendation, very low-quality evidence).

Only 1 trial (not identified in the 2008 edition of the ESPGHAN/ESPID guidelines) was found for activated charcoal. This RCT (n = 39; children ages 6 weeks to 10 years with AGE and severe dehydration), whose methodology is questionable (unclear randomization, allocation concealment, follow-up, and baseline comparability), found a significant reduction in the duration of diarrhea, and reduced ORS intake in the group receiving activated charcoal compared with the control group. There was no significant difference in the mean IV therapy requirement between the groups (170).

9.3.4 Antisecretory Drugs

Racecadotril

> Racecadotril can be considered in the management of AGE (II, B) (weak recommendation, moderate-quality evidence).

A recent individual patient data meta-analysis (146) assessed the efficacy of racecadotril as an adjunct to ORS compared with ORS alone or with placebo. Raw data from 9 RCTs involving 1348 children ages 1 month to 15 years with AGE were available for the analysis. The experimental treatment was compared with placebo, with no treatment (2 RCTs), and with kaolin–pectin (2 RCTs, the latter was not in line with the authors' objectives). There were 4 studies in the inpatient setting, and 5 studies in the outpatient setting. Compared with placebo, racecadotril significantly reduced the duration of diarrhea. Almost twice as many patients recovered at any time in the racecadotril group versus the placebo group ($P < 0.001$). There were no interactions between treatment and dehydration, rotavirus infection, type of study (outpatient/inpatient), or country. In the studies of inpatients, the ratio of mean stool output racecadotril/placebo was reduced ($P < 0.001$). In outpatient studies, the number of diarrheal stools was lower in the racecadotril group ($P < 0.001$). In the responder analysis (defined as a duration of diarrhea of <2 days), the proportion of responders was significantly higher in the racecadotril group than in the placebo group (50.3% vs 25.8%, respectively). By adjusting for dehydration and rotavirus, the absolute risk difference was 24.7% (95% CI 19.8–29.7), and the associated number needed to treat was 4. The secondary need for care in outpatients was significantly in favor of racecadotril in 2 studies. Also, the need for IV therapy was lower in the racecadotril group than in the placebo group. There was no difference in the incidence of adverse events between the groups.

Bismuth Subsalicylate

> Bismuth subsalicylate is not recommended in the management of children with AGE (III, C) (strong recommendation, low-quality evidence).

No new RCTs were identified.

Zinc

> Children age >6 months in developing countries may benefit from the use of zinc in the treatment of AGE; however, in regions where zinc deficiency is rare, no benefit from the use of zinc is expected (I, A) (strong recommendation, moderate-quality evidence).

Three new meta-analyses of the use of zinc for treating AGE in children have been published. The first one identified 18 RCTs, mostly performed in developing countries where zinc deficiency is common, involving 11,180 participants. The use of zinc was associated with a significant reduction in diarrhea duration and risk of diarrhea lasting >7 days, but not with a significant reduction in stool volumes (171). The second meta-analysis found that zinc supplementation reduced the mean duration of acute diarrhea by 19.7% (19 RCTs, n = 8957) and the mean duration of persistent diarrhea by 15% to 30%; however, zinc supplementation had no effect on stool frequency or stool output, and it increased the risk of vomiting (172).

A recent review (173) identified 24 RCTs comparing oral zinc supplementation with placebo in children ages 1 month to 5 years with acute diarrhea, who were mainly from developing countries wherein zinc deficiency is common. Interestingly, in children age <6 months, zinc supplementation did not affect the mean duration of diarrhea and it may increase the risk of diarrhea persisting until day 7. In children >6 months, zinc reduced the duration of diarrhea, and the risk of diarrhea persisting until day 7.

Only 1 RCT has been carried out in Europe. In this trial, 141 Polish children with AGE ages 3 to 48 months were randomized to receive zinc sulfate or placebo for 10 days. Diarrhea duration did not differ significantly between the groups ($P > 0.05$), neither did secondary outcome measures, namely, stool frequency on days 1, 2 and 3, vomiting frequency, IV fluid intake, and the number of children with diarrhea lasting >7 days (174). At least 1 large trial in a high-income country (USA) of oral zinc for the treatment of acute diarrhea is presently in progress (*clinicaltrials.gov* NCT01198587).

9.3.5 Probiotics

Active treatment with probiotics, in adjunct to ORS, is effective in reducing the duration and intensity of symptoms of gastroenteritis. Selected probiotics can be used in children with AGE (I, A) (strong recommendation, moderate-quality evidence).

New evidence has confirmed that probiotics are effective in reducing the duration of symptoms in children with AGE (I, A) (strong recommendation, moderate-quality evidence).

The use of the following probiotics should be considered in the management of children with AGE as an adjunct to rehydration therapy:

- *L rhamnosus* GG and *S boulardii* (I, A) (strong recommendation, low-quality evidence).

With regard to probiotics, these guidelines endorse the document developed by the ESPGHAN Working Group on Probiotics and Prebiotics, which provided recommendations for the use of probiotics for the treatment of AGE in infants and children (175). In brief, these recommendations were based on a systematic review of previously completed systematic reviews and of RCTs published subsequently to these reviews. Probiotics (as a group) reduced the duration of diarrhea by approximately 1 day; however, probiotic effects are strain-specific, so the efficacy and safety of each should be established. Moreover, the safety and clinical effects of 1 probiotic microorganism should not be extrapolated to other probiotic microorganisms. A lack of evidence regarding the efficacy of a certain probiotic(s) does not mean that future studies will not establish health benefit(s). For details, see Table 6. According to the ESPGHAN Working Group on Probiotics and Prebiotics, the use of the following probiotics may be considered in the management of children with AGE in addition to rehydration therapy: *L rhamnosus* GG (low-quality evidence, strong recommendation), *S boulardii* (low-quality evidence, strong recommendation), based on a consistent amount of evidence in various settings.

L reuteri DSM 17938 was also included in the list of strains recommended (weak recommendation, very low-quality evidence). Another heat killed *Lactobacillus* strain (*L acidophilus* LB), which cannot be defined a probiotic strain, demonstrated some efficacy in reducing AGE-related symptoms in pediatric age (weak recommendation, very low-quality evidence) (175).

9.3.6 Synbiotics

None of the synbiotics studied thus far can be recommended until confirmatory data are available (II, B) (weak recommendation, low-quality evidence).

Synbiotics were not addressed in the previous ESPGHAN/ESPID guidelines owing to lack of data. Three RCTs evaluated the efficacy of synbiotics for the management of AGE. The first RCT compared the efficacy of a combination of 5 probiotic strains (*Str thermophilus*, *L rhamnosus*, *L acidophilus*, *B lactis*, and *B infantis*) and fructooligosaccharides in 111 children with acute diarrhea (median age 40 months) (176). The median duration of diarrhea was significantly shorter in the synbiotic group than in the placebo group ($P < 0.005$). The number of children with normalized stool consistency was higher at day 2 ($P < 0.001$) and at day 3 ($P < 0.001$) in the synbiotic group than in the placebo group. Moreover, fewer additional medications (antipyretics, antiemetics, antibiotics) were administered in the synbiotic group.

In the second single-blinded RCT, which included 209 Turkish hospitalized children, the efficacy of treatment with *Lactobacillus acidophilus*, *L rhamnosus*, *Bifidobacterium bifidum*, *B longum*, and *Enterococcus faecium* at a dose of 2.5×10^9 CFU, and 625 mg fructooligosaccharide for 5 days was evaluated. Administration of the synbiotic mixture in addition to conventional rehydration therapy compared with rehydration only reduced the duration of diarrhea and the duration of hospitalization (177).

In the third RCT (178), which included 107 Italian children ages 3 to 36 months, another synbiotic combination (*L paracasei* B21060 plus arabinogalactan and xilooligosaccharides) also appeared to be beneficial. Resolution of diarrhea at 72 hours was significantly more frequent in children who received the synbiotic combination than in the placebo group ($P = 0.005$). Moreover, children in the synbiotic group experienced a significant reduction in the total duration of diarrhea ($P = 0.04$), number of stool outputs 48 to 72 hours after treatment ($P = 0.005$), and stool consistency score 48 to 72 hours after treatment ($P = 0.002$). The percentage of patients requiring hospitalization, percentage of parents that missed at least 1 working day, and rate of use of adjunct medications were also significantly lower in the synbiotic group.

9.3.7 Prebiotics

The use of prebiotics in the management of children with AGE is not recommended (II, B) (weak recommendation, low-quality evidence).

No new trials identified.

9.3.8 Micronutrients

Folic acid is not recommended for the management of children with AGE (II, B) (weak recommendation, very low-quality evidence).

9.3.9 Gelatine Tannate

Gelatine tannate is not recommended for the management of children with AGE (III, C) (weak recommendation, very low-quality evidence)

Gelatine tannate is a mixture of tannic acid and gelatin. Tannic acid has stringent properties owing to its capacity to form protein–macromolecular complexes, as well as antibacterial, antioxidant, and anti-inflammatory properties (179). One clinical trial (no randomization, no blinding, unbalanced baseline characteristics) in 211 children ages 3 months to 12 years with AGE (>3 liquid stools for <72 hours) found a significant decrease in stool number and

TABLE 6. Probiotics for treating acute gastroenteritis (recommendations developed by the ESPGHAN Working Group on probiotics/prebiotics)

Strain(s)	Quality of evidence	Recommendation	Dose
Probiotics with a positive recommendation			
LGG	Low	Strong	$\geq 10^{10}$ CFU/day (typically 5–7 days)
Saccharomyces boulardii	Low	Strong	250–750 mg/day (typically 5–7 days)
Lactobacillus reuteri DSM 17938	Very low	Weak	10^8–4×10^8 (typically 5–7 days)
Heat-killed *Lactobacillus acidophilus* LB*	Very low	Weak	Minimum 5 doses of 10^{10} CFU for 48 h; maximum 9 doses of 10^{10} CFU for 4.5 days
	Quality of evidence	Recommendation	Reason
Probiotics with a negative recommendation			
Enterococcus faecium (SF68 strain)	Low	Strong	Safety issues (a possible recipient of the vancomycin-resistance genes)
		Quality of evidence	Reason for a lack of recommendation
Probiotics with a lack of recommendation			
E coli Nissle 1917		Very low	Methodological issues
L acidophilus		Very low	No strain identification
L acidophilus rhamnosus 573L/1, 573L/2, 573L/3		Moderate	Only 1 RCT available
L paracasei ST11		Moderate	Only 1 RCT available
L acidophilus, *L rhamnosus*, *B longum*, *S boulardii*		Moderate	Only 1 RCT available; no strain identification
L helveticus R0052, *L rhamnosus* R0011		Very low	Only 1 RCT available
Bacillus mesentericus, *Clostridium butyricum*, *Enterococcus faecalis*		Very low	Only 1 RCT available; no strain identification
L delbrueckii var *bulgaricus*, *L acidophilus*, *Str thermophiles*, *B bifidum* (strains LMG-P17550, LMG-P 17549, LMG-P 17503, and LMG-P 17500)		Very low	Only 1 RCT available
Bifidobacterium lactis Bb12		No data	Lack of data
B lactis Bb12, *Str thermophiles* TH3		Very low	Only 1 RCT available
Bacillus clausii (O/C84, N/R84, T84, SIN84)		Low	Only 1 RCT available
L acidophilus, *L paracasei*, *L bulgaricus*, *L plantarum*, *B breve*, *B infantis*, *B longum*, *Str thermophiles*		Very low	Only 1 RCT available; no strain identification
L acidophilus, *B infantis*		Very low	No strain identification
L acidophilus, *B bifidum*		Very low	No strain identification

CFU = colony-forming unit; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; LGG = *Lactobacillus* GG; RCT = randomized controlled trial.
* This is not a probiotic strain being heat killed.

improvement in stool consistency in the group treated with ORS plus gelatin tannate compared with ORS alone (180).

9.4 Anti-Infective Therapy

Anti-infective therapy should not be given to the vast majority of otherwise healthy children with acute gastroenteritis (Va, D) (strong recommendation, low-quality evidence).

Acute gastroenteritis in a child without significant underlying disease is usually self-limited regardless of the etiologic microorganism, which is seldom known at the onset of symptoms. Even without specific antimicrobial therapy, clinical recovery generally occurs within a few days and the causative organism is cleared in a relatively short time, usually within a few days or weeks. Complications are uncommon.

9.4.1 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 (Va, D) (strong recommendation, low-quality evidence).

9.4.2 Pathogen-Based Approach

The etiological agents and antibiotic treatment of bacterial gastroenteritis are listed in Table 7.

Shigella Gastroenteritis

Antibiotic therapy is recommended for culture-proven or suspected *Shigella* gastroenteritis (II, B) (strong recommendation, moderate-quality evidence).

The first-line treatment for shigellosis is azithromycin for 5 days (II, B) (strong recommendation, moderate-quality evidence).

A meta-analysis of 16 studies, which included 1748 children and adults with *Shigella* dysentery, concluded that appropriate antibiotic therapy shortened the duration of the disease (181). Several well-designed controlled studies have shown that appropriate antibiotic treatment of *Shigella* gastroenteritis significantly reduced the duration of fever, diarrhea, and fecal excretion of the pathogen, and thus infectivity, which is extremely important in children attending day-care centers, in institutions and hospitals. Antibiotic treatment may also reduce complications including the risk of hemolytic–uremic syndrome after *S dysenteriae* 1 infection (182).

The WHO recommends that all episodes of *Shigella* infection be treated with ciprofloxacin or 1 of the 3 second-line antibodies (pivmecillinam, azithomycin, or ceftriaxone) (183). The major problem, however, is the increasing worldwide resistance of *Shigella* to antibiotics that is also being observed in Europe. Therefore, *Shigella* isolates should be tested for susceptibility, and local resistance patterns closely monitored. A systematic review of data from 1990 to 2009 identified 8 studies in children up to 16 years with shigellosis, reporting clinical failure 3 days after treatment. In addition 4 studies evaluated bacteriologic failure and 5 assessed bacteriologic relapse. Clinical failure rate was 0.1%, and bacteriologic relapse was 0.0%. Based on these figures, which however derive from low-income countries, antibiotic therapy is effective and strongly recommended in all of the children with shigellosis. It should be noted, however, that this finding has not been demonstrated in outpatients. Because of the high worldwide resistance, trimethoprim–sulfamethoxazole and ampicillin are recommended only if the strain isolated is susceptible, or if present local microbiologic data suggest susceptibility. A resistance rate of 12.8% to nalidixic acid was reported in Belgium (184). In Europe and the United States, resistance to ceftriaxone (185), azithromycin (186,187), and ciprofloxacin has been reported, but is uncommon (185,188).

The first-line oral empiric treatment recommended for *Shigella* gastroenteritis is azithromycin for 5 days, which was found

TABLE 7. Antibiotic therapy of bacterial gastroenteritis

Pathogen	Indication for antibiotic therapy	Drug of choice*	Alternative agents
Shigella spp	Proven or suspected shigellosis	Oral: azithromycin (12 mg/kg on day 1, followed by 6 mg/kg for 4 days); parenteral, IV, IM: ceftriaxone (50 mg/kg for 2–5 days)†	Cefixime (8 mg · kg^{-1} · day^{-1}); ciprofloxacin‡ PO (20–30 mg · kg^{-1} · day^{-1}). For a known susceptible strain: TMP/SMX† (8 mg · kg^{-1} · day^{-1} of TMP) or ampicillin (100 mg · kg^{-1} · day^{-1}) or nalidixic acid (55 mg · kg^{-1} · day^{-1})
Salmonella spp (nontyphoidal)	Antibiotic therapy is indicated only in high-risk children§ to reduce the risk of bacteremia and extraintestinal focal infections	Ceftriaxone (50–100 mg · kg^{-1} · day^{-1})	Azithromycin (10 mg · kg^{-1} · day^{-1}); ciprofloxacin‡ PO (20–30 mg · kg^{-1} · day^{-1}); for a known susceptible strain, TMP/SMX§ (8 mg · kg^{-1} · day^{-1} of TMP).
Campylobacter spp	Antibiotic therapy is recommended mainly for the dysenteric *Campylobacter* gastroenteritis and most efficacious when started within 3 days after onset of the disease	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days, or a single dose of 30 mg/kg)	Doxycycline (>8 years) or ciprofloxacin (>17 years), when susceptible)
Shiga toxin-producing *Escherichia coli*	Antibiotic therapy is not recommended	—	—
Enterotoxigenic; *Escherichia coli*	Antibiotic therapy is recommended, mainly for traveler's diarrhea	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days)	Cefixime (8 mg · kg^{-1} · day^{-1} for 5 days); TMP/SMX§ (8 mg · kg^{-1} · day^{-1} of TMP); ciprofloxacin§ PO (20–30 mg · kg^{-1} · day^{-1}); rifaximin (>12 years, 600 mg/day, for 3 days)
Vibrio cholerae	Antibiotic therapy is recommended for confirmed or suspected case by travel history	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days, or a single 20 mg/kg dose)	Doxycycline (>8 years), Ciprofloxacin (>17 years), or TMP/SMX§ (when susceptible)
Clostridium difficile	Antibiotic therapy is recommended for moderate and severe cases	Metronidazole (30 mg · kg^{-1} · day^{-1} for 10 days)	Vancomycin PO (40 mg · kg^{-1} · day^{-1})

PO = per os.
* Depends on local antibiotic susceptibility profile, which should be monitored.
† TMP/SMX, trimethoprim–sulfamethoxazole.
‡ Ciprofloxacin is usually not recommended in the pediatric age group, but it can be used in children <17 years when an alternative is not feasible.
§ See text.

to be more effective than either cefixime or nalidixic acid (189,190). Alternatively, nalidixic acid or cefixime can be administered, both for 5 days. When *Shigella* isolates are susceptible to trimethoprim–sulfamethoxazole and/or ampicillin (ie, in an outbreak setting), these agents are the recommended first-line treatment. Oral fluoroquinolones can be used in children age <17 years when no other alternative is feasible. The recommended first-line parenteral treatment is ceftriaxone for 5 days (191). 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 (192).

Salmonella Gastroenteritis

Antibiotic therapy is not effective on symptoms and does not prevent complications. It is associated with a prolonged fecal excretion of Salmonella. Therefore, antibiotics should not be used in an otherwise healthy child with *Salmonella* gastroenteritis (I, A) (strong recommendation, moderate-quality evidence).

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

A Cochrane systematic review showed that antibiotic therapy of *Salmonella* gastroenteritis does not significantly affect the duration of fever or diarrhea in otherwise healthy children or adults compared with placebo or no treatment Moreover, antibiotics were associated with a significant increase of carriage of *Salmonella*, although other adverse events were not reported. As secondary *Salmonella* bacteremia—with extraintestinal focal infections—occurs more often in children with certain underlying conditions, and in neonates or young infants (58), antibiotic therapy is suggested in these children to reduce the risk of bacteremia (Table 5).

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 reduces symptoms if instituted in the early stage of the disease (within 3 days after onset) (I, A) (strong recommendation, moderate-quality evidence).

The drug of choice is azithromycin, but antibiotic choice should be based on local resistance pattern (III, C) (weak recommendation, low-quality evidence).

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 (193). The effect was more pronounced if treatment started within 3 days of illness onset (193) and in children with *Campylobacter*-induced dysentery. In a parallel group, assessor-blind trial, testing for inequality in 130 children with *Campylobacter jejuni/coli* enterocolitis, azithromycin in a single dose of 30 mg/kg was more effective than erythromycin for 5 days, and the latter was of no benefit compared to placebo when started >60 hours of disease onset (194). Antibiotic treatment significantly reduces the duration of fecal excretion of *Campylobacter* spp, and thus its infectivity. It is unclear whether antibiotic treatment of *Campylobacter* gastroenteritis prevents the development of postinfectious Guillain-Barre syndrome. Azithromycin is the drug of choice in most locations, although local resistance patterns should be closely monitored (194).

Diarrheagenic E coli

Antibiotics should not be routinely given for AGE due to *E coli*. The treatment is nonspecific and administration of antibiotics could have adverse effect (Vb, D) (weak recommendation, very low-quality evidence).

Antibiotic therapy for Shiga toxin-producing *E coli* is not recommended (Vb, D) (strong recommendation, low-quality evidence).

Antibiotic therapy for enterotoxigenic *E coli* is recommended (II, B) (strong recommendation, moderate-quality evidence).

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 duration of fecal excretion of the pathogen. As 2 case-controlled studies obtained conflicting results about antibiotic treatment of STEC gastroenteritis and the risk of developing hemolytic-uremia syndrome (195,196), this issue is currently unclear and not routinely indicated. Antibiotic treatment of gastroenteritis caused by enterotoxigenic *E coli* or by enteropathogenic *E coli* significantly shortens the clinical course (mainly the duration of diarrhea) and fecal excretion of the pathogen. Rifaximin, a broad-spectrum, nonabsorbed antimicrobial agent, can be used in children >12 years for nonfebrile watery diarrhea presumably caused by enterotoxigenic (197,198) or enteroaggregative *E coli* gastroenteritis (199).

C difficile

This is an emerging agent of diarrhea whose role is limited or questionable in children age <36 months. It is also a major agent of antibiotic induced diarrhea and of severe diarrhea in children with underlying chronic conditions such as IBDs. Hypervirulent strains may induce severe symptoms and should be treated with oral metronidazole or vancomycin (200). Antibiotic-associated diarrhea is often caused by *C difficile*. Mild disease often resolves by discontinuation of the antibiotic used. For moderate or severe disease, the first-line treatment is oral metronidazole ($30\ mg \cdot kg^{-1} \cdot day^{-1}$); oral vancomycin is reserved for resistant strains (19).

Other Causes of Bacterial Gastroenteritis

Antibiotic therapy is recommended for *Vibrio cholerae* gastroenteritis (II, B) (strong recommendation, moderate-quality evidence).

Appropriate antibiotic treatment of cholera reduces the durations of diarrhea by approximately 50% and fecal shedding of *V cholerae* by approximately 1 day. WHO recommends administration for 3 to 5 days of furazolidone, trimethoprim–sulfamethoxazole, or erythromycin to children <8 years and of

tetracycline to older children. A randomized, controlled study demonstrated that a single 20 mg/kg azithromycin dose is more efficacious clinically and microbiologically than ciprofloxacin (201); it is the drug of choice for children age <8 years. Alternative treatment for older children is doxycycline. Trimethoprim–sulfamethoxazole can be used for susceptible 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*.

Antibiotic therapy is not generally needed for antibiotic-associated diarrhea, but should be considered in moderate-to-severe forms (Vb, D) (weak recommendation, very low-quality evidence).

Antibiotic-associated diarrhea can be defined as change in normal stool frequency with at least 3 liquid stools/day for 1 (WHO) or 2 consecutive days (202–206) for which no other cause can be identified (intercurrent viral or bacterial infection, laxative use, other cause) and microbiological investigations for *C difficile* are negative (207). It occurs during (early onset) or 2 to 6 weeks after (late onset) antibiotic treatment (204,208).

9.4.3 Empiric Antibiotic Therapy in Sporadic Cases of AGE

The choice of the antimicrobial agent depends on the local prevalence of the 3 pathogens (*Shigella* spp, *Campylobacter* spp, and *Salmonella enterica*) and the resistance patterns (Va, B) (strong recommendation, moderate-quality evidence).

In children with watery diarrhea, antibiotic therapy is not recommended unless the patient has recently traveled or may have been exposed to cholera (Vb, D) (strong recommendation, moderate-quality evidence).

Bloody diarrhea with low or no fever is typical of STEC (enterohemorrhagic *E coli*), but can be mild shigellosis or salmonellosis. Antibiotics are not recommended unless epidemiology suggests shigellosis (Vb, D) (weak recommendation, low-quality evidence).

Parenteral rather than oral antibiotic therapy is recommended (Va, D) (strong recommendation, low-quality evidence) 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, suspected or confirmed bacteremia
4. Neonates and young infants (<3 months) with fever. Sepsis workup and antibiotics should be considered according to local protocols

The cause of sporadic AGE is usually not known at presentation. The classification of these cases into invasive (or inflammatory) and watery (or noninvasive) may help deciding whether or not to start empiric antibiotics. Invasive 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*.

9.4.4 Antimicrobial Therapy of Systemic Infections Cause by Enteric Pathogens or Involvement of Extraintestinal Organs

Antibiotic therapy is recommended for the rare but severe extraintestinal infections caused bacterial enteric pathogens (Vb, D) (strong recommendation, low-quality evidence).

Occasionally enteric bacterial pathogens can spread and cause extraintestinal infections, including bacteremia or focal infections. These infections should be treated with antibiotics, usually parenterally.

9.4.5 Antimicrobial Therapy of Parasite-Induced Gastroenteritis

Antiparasitic treatment is generally not needed in otherwise healthy children; however, it may be considered if symptoms are severe (III, C) (strong recommendation, very low-quality evidence).

Severe cases of giardiasis can be treated with metronidazole, nitazoxanide, albendazole, or tinidazole (III, C) (weak recommendation, low-quality evidence).

Cryptosporidiasis should be treated mainly in immunocompromised children with nitazoxanide (III, C) (strong recommendation, low-quality evidence).

Amebic colitis should be treated with metronidazole (III, C) (strong recommendation, low-quality evidence).

Giardia is rarely involved in AGE, but the parasite should be treated if there is evidence of its active role in producing symptoms. Metronidazole (10 mg/kg 3 times daily for 7–10 days) remains the first-line treatment (209). Albendazole (once daily for 5 days) is probably as effective as metronidazole in achieving parasitological cure, but trials were performed in children with polyparasitism. A recent trial in adults with *Giardia* monoinfection showed equivalence of the 2 drugs in terms of parasitological cure and improving symptoms (210). Tinidazole (single dose) had similar results; nitazoxanide was found to be less effective (209,211).

Acute gastroenteritis due to *Cryptosporidium* spp in children with normal immunity is generally self-limited and most patients require only oral rehydration (22,212). Cryptosporidiosis is an important cause of morbidity in malnourished or HIV-positive children.

During outbreaks in hospitals or day-care centers, hygienic measures and prevention are probably as important as antimicrobial treatment (22). Nitazoxanide is recommended for AGE diarrhea caused by *Cryptosporidium* sp (213,214) but is not available in many countries.

In diarrheic children returning from endemic areas, laboratories must distinguish between *Entamoeba dispar* (nonpathogenic) and *E histolytica*, which requires rapid treatment with metronidazole.

9.4.6 Antiviral Treatment

Specific antiviral treatment is usually not indicated in AGE (Vb, D) (strong recommendation, very low-quality evidence).

Severe cytomegalovirus colitis, especially in an immunocompromised child, should be treated with ganciclovir (III, C) (strong recommendation, low-quality evidence).

Oral immunoglobulin may be considered in children hospitalized with rotavirus gastroenteritis (III, C) (weak recommendation, very low-quality evidence).

Viruses are the leading cause of AGE, and usually have an acute and self-limiting course; however, selected patients and/or severe infection may need specific treatment. Consistent evidence demonstrated that oral administration of immunoglobulin (300 mg/kg) may be beneficial for rotaviral infection and is associated with a faster recovery from acute diarrhea (215,216), and permanent clearance of the virus in immunocompromised children (217). More recently, hyperimmune immunoglobulins Y (IgY) produced from poultry hens were found to be strongly reactive to several rotavirus serotypes. Oral administration of IgY could improve clinical outcomes even for patients with mixed enteric infections, and is a useful adjunct to general supportive therapy in pediatric patients (218).

Oral immunoglobulin treatment has been proposed for norovirus enteritis. Resolution of diarrhea and decreased stool output were observed at 7 days, but no benefit was found for length of hospital stay or hospital cost (219).

Cytomegalovirus infection may have a severe course with extended intestinal involvement (usually severe colitis); it generally occurs in children with congenital or acquired immunodeficiency, and in transplant recipients. Ganciclovir therapy has been effective in treating and preventing cytomegalovirus infection in immunocompromised hosts (220); however, although the most appropriate treatment of isolated cytomegalovirus enterocolitis in immunocompetent subjects has yet to be determined, infants with severe clinical features could benefit from ganciclovir therapy (221).

9.4.7 Nitazoxanide for Rotavirus Diarrhea

There is insufficient evidence to recommend nitazoxanide in the management of children with rotavirus AGE until confirmatory data are available (III, C) (strong recommendation, low-quality evidence).

One single-blind (blinding of participants only) RCT (n = 75) conducted in Bolivia evaluated the effectiveness of oral or systematic rehydration versus the same intervention plus nitazoxanide or plus a probiotic preparation (*L acidophilus*, *L rhamnosus*, *B longum*, and *S boulardii)* in children ages 28 days to 24 months with rotavirus-positive watery diarrhea of <72 hours' duration, and a moderate-to-severe degree of dehydration (222). The recorded outcomes were duration of fever, hospitalization, and diarrhea. Also the time from the first dose to the first soft stool was reported for the nitazoxanide and probiotic groups. The groups were not comparable at baseline (eg, age). Mean durations of diarrhea and of hospitalization were significantly shorter in the nitazoxanide group than in controls.

A tabular summary of all of the ESPGHAN/ESPID recommendations on the management of acute gastroenteritis can be found at *http://links.lww.com/MPG/A317*.

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