Evidence-based path in pediatric infectious diseases: from guidelines to quality improvement

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INDEX

CHAPTER 1.
BACKGROUND AND AIMS

1.1 Background ........................................ Page 5
1.2 The quality of guidelines ....................... Page 5
1.3 Implementation of guidelines ................. Page 6
1.4 Guidelines in pediatric infectious diseases Page 8
1.5 Aims and overview of the thesis .......... Page 8
1.6 References ........................................ Page 11

CHAPTER 2.
PRODUCTION OF THE ESPGHAN/ESPID GUIDELINES FOR THE MANAGEMENT OF ACUTE GASTROENTERITIS IN EUROPEAN CHILDREN

2.1 Guidelines for the management of acute gastroenteritis and its role in clinical practice Page 13
2.2 Methodology for guidelines production .... Page 14
2.3 Major changes in the recommendations for the management of childhood diarrhea: 2014 guidelines update Page 17
2.4 References ........................................ Page 21
2.5 Publications .................................... Page 26

CHAPTER 3.
THE IDENTIFICATION OF RELEVANT CLINICAL OUTCOMES IN INFECTIOUS DISEASES

3.1 The Consensus Group on Outcome Measures Made in Pediatric Enteral Nutrition: COMMENT Initiative Page 65
3.2 Results of the COMMENT working group on respiratory infections Page 67
3.3 Results of the COMMENT working group on acute diarrhea Page 70
3.4 References ........................................ Page 72
3.5 Publications .................................... Page 73
CHAPTER 4.
ADHERENCE TO EUROPEAN GUIDELINES FOR ACUTE GASTROENTERITIS

4.1 Rationale and adherence to guidelines for acute gastroenteritis  Page 89
4.2 Methodology  Page 90
4.3 Results of a national multicenter observational study  Page 96
4.4 Discussion  Page 105
4.5 References  Page 109
4.6 Publication  Page 112

CHAPTER 5.
IMPLEMENTATION OF EFFECTIVE PROBIOTIC STRAINS FOR THE MANAGEMENT OF CHILDREN HOSPITALIZED FOR ACUTE GASTROENTERITIS

5.1 Rationale and identification of the clinical problem  Page 118
5.2 Evidence in support to the use of *Lactobacillus rhamnosus* GG for the treatment of children hospitalized for acute diarrhea  Page 118
5.3 Intervention to implement the use of *Lactobacillus rhamnosus* GG in a tertiary care children’s hospital  Page 121
5.4 Results of the rapid implementation program  Page 125
5.5 References  Page 128
5.6 Publications  Page 131

CHAPTER 6.
E-LEARNING AS A TOOL FOR IMPLEMENTATION OF CLINICAL GUIDELINES ON ACUTE GASTROENTERITIS

6.1 Rationale of the initiative  Page 147
6.2 E-learning instrument and methodology  Page 149
6.3 Results of the implementation of the ESPGHAN e-learning course on acute gastroenteritis  Page 152
6.4 Discussion  Page 159
6.5 Spreading the e-learning initiative to developing countries: the FISPZGHAN working group on acute diarrhea  Page 160
6.6 References  Page 161
CHAPTER 7.
QUALITY CARE IMPROVEMENT TO REDUCE INFECTIONS IN CHILDREN WITH LEUKEMIA

7.1 Rationale
Page 161
7.2 Methodology
Page 162
7.3 Results of the implementation program
Page 167
7.4 Discussion
Page 174
7.5 References
Page 177

CHAPTER 8.
CONCLUDING REMARKS

8.1 Conclusions
Page 181
8.2 References
Page 184

CHAPTER 9.
CURRICULUM VITAE

9.1 Curriculum vitae
Page 185
9.2 Role in Scientific Societies and Working Groups
Page 193
9.3 Awards
Page 193
9.4 Grants
Page 194
9.5 Teaching Activities
Page 194
CHAPTER 1.

BACKGROUND AND AIMS

1.1 Background

Clinical practice guidelines (CPGs) are systematically developed statements to assist practitioners in making decisions about appropriate health care in specific clinical circumstances [1]. Their purpose is to make explicit recommendations with a definite intent to influence what clinicians do. Clinical practice guidelines currently represent the standard of care and a support for medical practitioners for the management of different acute and chronic conditions in different period of life from infancy to elderly.

The primary goal of CPGs in pediatrics is to improve the health of infants and children by ensuring that they receive up-to-date, evidence-based care.

However the process that leads from the identification of clinical problem to the delivery of standard care to the target population is complex and time-consuming. It includes many different steps from the development of clinical recommendations to their dissemination and local implementation (Figure 1.1), and each of these steps is needed to ensure a rapid application of evidence-based recommendations.

In the last 20 years the number of this kind of CPGs is progressively increasing in international literature, including in the field of pediatrics. However, the plethora of CPGs has been accompanied by growing concern about differences among clinical recommendations and about the quality of guidelines [2-5].

1.2 The quality of guidelines

How does one define the quality of guidelines? A “good” guideline should be scientifically valid, usable, reliable, and should improve the outcome of patients. However, it is rarely known how a guideline performs in clinical practice. Evaluation of CPGs should include both methods used to develop recommendations and applicability of recommendations (benefits, adverse effects and costs) [6].

An international group of researchers, the Appraisal of Guidelines, Research and Evaluation (AGREE) Collaboration, developed and validated a specific instrument to assess the quality of CPGs
based on theoretical assumptions [7], in 2010 the same group of expert developed a new updated version of this instrument [8].

A recent assessment of the quality of pediatric guidelines with the AGREE instrument demonstrated better results for CPGs produced in the field of pediatrics than those addressed to adult conditions [9]. In addition, the endorsement of leading Institutions or Scientific Societies such as the American Academy of Pediatrics or the registration in the National Guidelines Clearinghouse represent a guarantee of quality in most of cases.

We previously used this instrument to assess the quality of guidelines on acute gastroenteritis in children, and to identify weaknesses and strengths, with the ultimate aim of improving the quality and applicability of guidelines produced in this filed [6].

According to the AGREE criteria, the overall quality of published CPGs devoted to acute gastroenteritis was fair, and, among the nine documents included in the analysis, only three were strongly recommended without any provisos or alteration.

Aims, target population, synthesis of evidence, formulation of recommendations and clarity of presentation are points of strength.

The involvement of professionals and users in the steering group is a point of strength in the development process, however in our analysis all the CPGs but two failed to provide information about patients preferences/expectations and experiences. Patient’s dimension should be factored into decisions regarding clinical care, and this is particularly true for common diseases such as acute infectious diarrhea.

Other relevant weak issues are applicability, including identification of organizational barriers and adherence parameters, and cost/efficacy analysis.

The AGREE is also used during the development of a new guidelines to draw the frame of the document and to define the quality criteria on which a high-quality CPGs should be built.

According to our data, the quality of CPGs for the management of acute gastroenteritis improved during the time and mainly after the publication of the paper describing the AGREE-instrument and domains of improvement were those related to methodology and editorial independence. This may suggest that compliance with validated criteria may contribute to development of high quality guidelines.

1.3 Implementation of guidelines
High-quality CPGs are a major tool to improve quality of care [10, 11]. However the development of CPGs is not enough and pilot testing, capillary dissemination and local implementation are critical steps to change clinical practice.

For many health conditions, there is a gap between what medical science has shown to be effective practice and what is actually done [12].

Strong evidence reports that compliance with guideline recommendations is often poor in different medical settings and a high rate of inappropriate medical interventions has been reported for different clinical condition in pediatric age.

Two relevant papers published in the New England Journal of Medicine showed a poor adherence to standard of care both in adults and pediatric population in United States [13, 14]. According to these data, about half of patients receive evidenced-based care, and a large proportion of patients receive everyday low quality care, not-recommended medications, unnecessary diagnostic and medical interventions. This seems to be true for the management of both acute and chronic conditions, and even in case of prevention strategies.

The deficits that the authors identified in adherence to recommended processes for basic care pose serious threats to the health of the American public. A similar deficit in the quality of care was reported in the management and prevention of pediatric diseases [14].

The authors of both papers concluded with a call for strategies to reduce the apparent deficits in quality of delivered care.

Local implementation of CPGs and adherence to clinical recommendations has been demonstrated effective in reducing inappropriate medical intervention and the number of visits, hospitalizations and costs in children.

Implementation and dissemination strategies affect the probability of guidelines of being effective [15]. Implementation depends on acceptance of specific recommendations by physicians, and on the applicability of indications and acceptance by customers. Only a minority of physicians fully complies with guidelines. To increase compliance, experts recommend that guidelines should be tested in local settings [16-18]. Although AGREE requires guideline committees to undertake pilot testing before publication to ensure that the guideline can be put into practice, only few CPGs usually report this point in the document.

In addition, the process of CPGs development should consider potential barriers to implementation and provide monitoring criteria to assess guideline’s impact.
1.4 Guidelines in pediatric infectious diseases

The infectious diseases are the most common illnesses in infants and children. Respiratory and gastrointestinal infections represent the major indication to medical visit, access to emergency department and hospital admission in pediatric age worldwide.

The melting pot of pediatric infectious diseases includes many different conditions that ranges from acute, self-limiting and easy-to-mange illnesses (eg. flu-like illness, acute gastroenteritis) to severe or chronic and life-threatening conditions such as HIV infection, tuberculosis or opportunistic infections in at-risk or immune-compromised subjects. With few exceptions, infectious diseases are curable if an accurate and rapid diagnosis is performed and the appropriate treatment is provided. In addition, all these conditions, although with different rates, have high social and economic burden.

Many different CPGs for the prevention and management of selected infectious conditions have been produced and are continuously updated. The routine and correct application of evidence-based recommendations may potentially have a dramatic impact on the burden of all infections in pediatric age, improving child health and reducing inappropriate interventions, adverse effects and health-care expenses.

For all these reasons, and from a methodological point of view the infectious diseases represents an ideal setting to test the efficacy and applicability of CPGs.

1.5 Aims and overview of the thesis

This thesis depicts the entire evidence-based path that leads from the rigorous process of guidelines development to the final step of local implementation of clinical recommendations.

The overall aims of this work are:

1) To describe the process guidelines development and assessment of quality of scientific evidence for the management of specific infectious diseases in pediatric age (i.e. acute gastroenteritis);

2) To describe the methodology for the identification of relevant outcome measures in the field of pediatric infectious diseases;

3) To assess the appropriateness of medical interventions and quality of care delivered to children with selected infectious diseases (i.e. acute gastroenteritis);
4) To test the efficacy and effectiveness of different interventions for the implementation and local tailoring of recommendations for the management of infectious diseases in children.

To reach these objectives and describe the evidence-based process the thesis reports the results of different works organized as follows:

- The evaluation of the quality of scientific evidence on the acute gastroenteritis as basis for the development of the new up-dated European evidence-based guidelines for the management of acute gastroenteritis in children. In addition, the same process leaded the publications of two reviews reporting the hospital management of children with acute diarrhea and exploring the differences between evidence-based recommendations and clinical practice in children living in developed and developing areas (chapter 2);

- The identification of relevant clinical outcomes for the production of a core-outcome set to standardize the evaluation of efficacy of different interventions aimed at reducing the impact of infectious diseases (i.e. respiratory infections and acute diarrhea) and to drive future clinical trials in the field (chapter 3);

- The assessment of quality of care delivered to children hospitalized for acute intestinal infections in Italian institutions through the design of a multicenter observational study carried out in more than 30 pediatric wards (chapter 4);

- The identification of effective interventions to promote the use of Lactobacillus GG to reduce the duration of diarrhea in children admitted for acute gastroenteritis and local implementation in a tertiary-care children hospital in United States (chapter 5);

- An intervention trial aimed at evaluating the impact of an e-learning course on the knowledge and clinical practice of pediatricians and family physicians in 15 European countries (chapter 6);

- A quality care improvement study aimed at reducing the incidence and severity of infectious events, mainly central-line associated blood stream infections in children with acute leukemia.
Figure 1.1 Evidence-based path: from the production to implementation of guidelines
1.6 References


2.1 Acute gastroenteritis in childhood and the need for a European guideline

Acute gastroenteritis (AGE) still represents a common cause of morbidity and mortality among infants and children worldwide. In developing areas the rapid fluid loss related to acute diarrhea, vomiting and fever, together with the difficult to oral rehydration and the limited access to clean water and facilities, gives to AGE the second leading position among the causes of child death.

In industrialized countries, the disease is relatively mild and generally self-limiting, but nevertheless can have a major impact on the quality of life of infected children and their families. In these areas, AGE represents a major cause of outpatient visits and hospital admissions and consequently it has a substantial effect on health-care expenses.

Before the large dissemination of rotavirus vaccines, in United States AGE determined about 1.5 million outpatient visits and over 200,000 hospitalizations every year [1].

Several guidelines for the management of AGE in children are available. However, only a minority of physicians fully complies with guidelines, and clinical recommendations are only slowly put into practice [2-5]. More specifically, the adherence to standard of care for AGE in United States is far from optimal, ranging from 37% in outpatients setting [6] to 69% in hospitalized children [7].

However, a higher compliance to guidelines recommendations for AGE can reduce the economic burden of the illness [7] and improve the clinical outcomes, by shortening the duration of diarrhea and enhancing weight gain [8].

The management of AGE essentially consists of the replacement of fluids lost through diarrheic stools, vomiting and fever. However, rehydration therapy does not reduce the severity not even the duration of intestinal symptoms [9]. With the overall aim of reducing the clinical and social burden of the illness, numerous anti-diarrheal drugs with different mechanism of action have been tested worldwide.
Europe encompasses a large number of countries that differ in terms of tradition, culture, wealth and health care systems. The management of AGE is significantly affected by all these social and economic aspects and covers today a broad range of interventions. All European children are expected to present at least 1 or 2 episodes of AGE every year below 5 years of age.

In the attempt to reduce the intensity and duration of symptoms related to AGE, in several countries, there is an excess of medical interventions that do not always result in clear beneficial outcomes. New options in terms of diagnosis, nutritional interventions, drugs, and prevention through the distribution of new vaccines against Rotavirus infection are becoming available. All these interventions may influence the severity and duration of symptoms and the rate of infection.

In 2008 a joint committee of experts belonging to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and to the European Society of Pediatric Infectious Diseases (ESPID) developed two evidence-based guidelines for the management of AGE in European children [10] and for the use of vaccines against Rotavirus infection in children [11]. These documents were addressed to practitioners at all levels of health-care, primary care physicians, pediatricians and family physicians in Europe.

The collaboration between the Societies was triggered by the understanding that AGE is still today a major pediatric health problem in all European countries. These two documents represented a milestone for the care of European children with AGE in the last 5 years and have had a major impact as judged by the number of citations (about 300) and by several papers addressing their quality and impact [12, 13].

2.2 Methodology for guidelines production

As stated in the 2008 version, an update accounting for scientific evidence accumulated over the last years was planned after 5 years since the publication of the guidelines.

This update used the same methodology reported in the previous version, however some difference in the process were applied and specifically described below.

The process started with specifying clinical questions that define the target population for search purposes defined as: previously healthy children 5 years of age or younger with clinically
diagnosed AGE (diarrhea and/or vomiting presumably of infectious origin), in- or outpatients living in geographic Europe.

However, since selecting evidence referred to this age group was not always possible in systematic reviews, in some cases, the data obtained in individuals up to age 18 were included. Children with at risk conditions, such as chronic disorders or immunodeficiency were not included. The process continued through a rigorous review of available scientific data (focusing on the last 5 years), the grading of evidence and the production of tables of evidence that are the prerequisite for a state-of-the-art evidence-based document.

The authors of each section of the guidelines conducted a literature search using primarily the MEDLINE and the Cochrane Library databases to identify relevant literature in English; however, relevant papers in other languages were also considered in some instances. When data referring to Europe were missing or limited, the search was extended to non-European settings, including developing countries.

In May 2013, the guideline development group met in Milan to discuss the outcome of the literature search and a first proposal of clinical recommendations. After a thorough discussion of each statement/question, the strength of recommendations and the strength of the supporting evidence were graded according to the Muir-Gray & Cook methodology (Table 2.1).

The present document differs from the 2008 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 (Table 2.2) [14]. However, to reflect the changes that have occurred, we have retained and revised the Muir-Gray and Cook rating that we used five years ago [15, 16].

The rationale for using the GRADE system was based on the fact that it is considered the most effective method of connecting evidence to clinical recommendations and is increasingly being applied by guideline development groups. In brief, the GRADE system offers four categories of quality of evidence (high, moderate, low, and very low) and two categories of the strength of recommendations (strong or weak) (Table 2.2).

Recommendations were formulated and graded, and a consensus was reached. Any disagreement was resolved by discussion until a consensus was reached. The draft of the guidelines was sent to the group members for review and further comments. All critical feedback was discussed and changes were incorporated as necessary. Finally, the guidelines were submitted for external peer review and then approved by the ESPGHAN and ESPID Council.
**Table 2.1.** Strength of evidence and grade of recommendations in support of the recommendations formulated in the 2008 ESPAGHAN/ESPID Guidelines for the Management of AGE in Children in Europe

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>I</th>
<th>Strong evidence from ≥1 systematic review(s) of well-designed RCTs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>Strong evidence from ≥1 properly designed RCT(s) of appropriate size.</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Evidence from well-designed trials without randomization, single group pre-post, cohort, time series, or matched case-control studies.</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Evidence from well-designed trials, non-experimental studies from &gt;1 center or research group.</td>
</tr>
<tr>
<td></td>
<td>Va</td>
<td>Opinion of respected authorities.</td>
</tr>
<tr>
<td></td>
<td>Vb</td>
<td>Clinical evidence, descriptive studies, or reports of expert committees.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>A</th>
<th>Supported by level I evidence, highly recommended.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Supported by level II evidence, recommended.</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Supported by level III evidence, recommended.</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Supported by level IV and V evidence; the consensus route would have to be adopted.</td>
</tr>
</tbody>
</table>

**Table 2.2.** The GRADE system

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>High quality</th>
<th>Further research is unlikely to change our confidence in the estimate of effect.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate quality</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td></td>
<td>Low quality</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td></td>
<td>Very low quality</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Strong</th>
<th>When the desirable effects of an intervention clearly outweigh the undesirable effects, or they clearly do not.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weak</td>
<td>When the trade-offs are less certain (either because of the low quality of evidence or because the evidence suggests that desirable and undesirable effects are closely balanced).</td>
</tr>
</tbody>
</table>
2.3 Major changes in the recommendations for the management of childhood diarrhea: 2014 guidelines update

Acute gastroenteritis still has a major impact in developed countries. The guidelines produced by ESPGHAN and ESPID Societies in 2008 drove the clinical practice all around Europe, in the last years. The management of AGE didn’t change dramatically, however an update of data on epidemiology, diagnostic workup and treatment was needed and scheduled 5 years after the publication of the first document. The continuous up-to-date of evidence is a necessary process to improve clinical practice. Major changes between 2008 and 2014 versions of ESPGHAN guidelines are reported in Table 2.3.

Epidemiology

This new version of guidelines reported new data on the epidemiology that slightly changed in the last times. Rotavirus is still the most common cause of AGE in children in all European countries, with an incidence as high as 1.33-4.96 cases/100 person year. Hospitalization rates for rotavirus gastroenteritis ranged from 7% to 81% in various countries. This rate had a major impact on costs [17]. Rotavirus serotype predominance appears to change on a seasonal basis within each country and may even differ between regions of the same country.

It’s well known that beginning from the 2006 two oral live rotavirus vaccines, Rotarix® and RotaTeq® have been licensed in Europe after the demonstration of their good safety and efficacy profiles in large clinical trials [18, 19].

Vaccination coverage in European countries is still low, and to date only few countries (Finland, Austria and Belgium) reported a coverage higher than 90% [20]. However, some changes in AGE epidemiology have been reported in countries where a rigorous implementation campaign of rotavirus vaccination has been promoted by the national institutions. In fact, the proportion of new (G12) or selected (G2P4) strains increased in countries after the introduction of vaccination [21, 22].

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 [23, 24]. Noroviruses represent 10-15% of causes of hospitalizations for AGE in European children.

In addition changes in bacterial and protozoal AGE have been reported in different countries with a reduction in Salmonella and Campylobacter and a rapid increase of Clostridium difficile infection
in selected settings, such as in United States where it has been related to community-acquired acute diarrhea even in low-risk pediatric populations [25, 26].

**Diagnostic work-up**

In otherwise healthy children with AGE, investigations are generally not needed. Dehydration reflects severity of illness and should be monitored by established score systems. Since 2008, a number of studies were conducted in children 1 to 36 months with AGE to validate the Clinical Dehydration Scale (CDS) [27]. The scale 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 three categories were: no dehydration (CDS score: 0), some dehydration (CDS score: 1-4), and moderate/severe dehydration (CDS score: 5-8) [28]. Successively this scale was validated in several clinical studies and it was found to be useful in predicting the need for intravenous rehydration [29, 30], weight gain [30], need for blood test [30, 31], need for hospitalization [30], the length of stay in hospital and in the ED [29, 31]. In addition, a fairly good inter-observer reliability was reported for CDS [30, 32].

**Diet and oral rehydration**

Oral rehydration with hypo-osmolar solution is the major treatment and should start as soon as possible. The so-called ESPGHAN oral rehydration solution containing 60 mmol Na⁺ is still the first treatment choice for European children. In breast-fed infants, breastfeeding should not be interrupted during AGE episode. Regular feeding should continue with no dietary changes including milk. Recent data based on a Cochrane systematic review suggest that in the hospital setting, in non-breast-fed infants and young children with severe AGE, lactose-free feeds can be considered in the management of gastroenteritis to reduce the duration of diarrheal episodes of about 18 hours [28, 33].

**Hospital management**

This version of European guidelines includes a completely new section on hospital management of children with severe AGE. Hospitalization should generally be reserved for children requiring enteral/parenteral rehydration; most cases may be managed in an outpatients setting. Despite the high number of hospitalization for AGE registered in all countries, yet a standardized rehydration scheme is not available. The guidelines provided an accurate and updated protocol for
the intravenous rehydration treatment [28]. In the last years rapid rehydration regimens have been proposed with the aim of reducing hospital stay and health-care expenses. In any case the level of evidence in support is still very low, and further studies in that field are needed to better define the ideal modality of rehydration.

Rehydration therapy through nasogastric tube is better than intravenous rehydration, in children with moderate-severe dehydration base on meta-analysis results [34, 35]. In any case the level of evidence in support is still very low, and further studies in that field are needed to better define the ideal modality of rehydration.

Intravenous rehydration is rarely needed; guidelines recommend intravenous rehydration in case of severe dehydration and/or in case of oral rehydration failure.

Despite the lack of evidence of efficacy, in the last years a rapid rehydration scheme (40-60ml/kg normal saline bolus over 60 minutes) has been gradually incorporated into clinical practice with the aim to obtain a reduction of symptoms, an improvement of appetite, and a reduction of hospital stay and of global costs of AGE. A survey of North American physicians, specialized in pediatric emergency, found that several regimens are used [36].

Ultrarapid rehydration proposed either by enteric or intravenous route demonstrated no difference in clinical outcomes, however reduced rehydration times are associated with high readmission rates and side effects.

**Antiemetics and Anti-diarrheal drugs**

Active therapy may reduce the duration and severity of diarrhea. Effective interventions include administration of specific probiotics such as *Lactobacillus GG* or *Saccharomyces boulardii* or anti-diarrheal drugs such as Diosmectite (an absorbent clay) or Racecadotril (an antisecretory drug). Anti-infectious drugs should be given in exceptional cases being viruses the leading cause of AGE.

Since vomiting is still a major indication to emergency department consultation and hospital admission and represents the most scaring AGE-related symptoms from physicians and families, stopping vomiting is one of the main issues in the management of AGE.

Antiemetics may reduce the need of intravenous rehydration because of vomiting and the number of hospital admission. The use of Ondansetron is supported by strong evidence of efficacy [37 - 39], but its routine use requires safety clearance given the warning about severe cardiac effects.
Table 2.3 Summary of major changes in guidelines recommendations – 2014 update.

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>2008</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of AGE</td>
<td>No change</td>
<td>Changes in countries where RV vaccination as been implemented</td>
</tr>
<tr>
<td>Etiology</td>
<td>RV, Norovirus</td>
<td></td>
</tr>
<tr>
<td>Dehydration scores</td>
<td>No recommendation</td>
<td>Clinical Dehydration Scale</td>
</tr>
<tr>
<td></td>
<td>Gorelick and Steiner scales suggested</td>
<td></td>
</tr>
<tr>
<td>Nutritional intervention</td>
<td>Not recommended</td>
<td>Lactose free diet to be considered in children hospitalized for severe AGE</td>
</tr>
<tr>
<td>Oral rehydration</td>
<td>Hypo-osmolar ORS recommended</td>
<td>Hypo-osmolar ORS recommended</td>
</tr>
<tr>
<td>Enteral rehydration</td>
<td>To be considered in selected cases</td>
<td>Superior to IV rehydration</td>
</tr>
<tr>
<td>Intravenous rehydration</td>
<td>-</td>
<td>Rapid rehydration recommended</td>
</tr>
</tbody>
</table>

**PHARMACOLOGICAL TREATMENT**

<table>
<thead>
<tr>
<th>Antiemetics</th>
<th>Not recommended</th>
<th>Ondansetron to be considered in selected cases after safety release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Not routinely recommended</td>
<td>Not routinely recommended</td>
</tr>
<tr>
<td>Probiotics</td>
<td>To be considered in addition to ORS</td>
<td>To be considered in addition to ORS New evidence in support</td>
</tr>
<tr>
<td>Racecadotril</td>
<td>To be considered in addition to ORS</td>
<td>To be considered in addition to ORS New evidence in support</td>
</tr>
<tr>
<td>Smectite</td>
<td>To be considered in addition to ORS</td>
<td>To be considered in addition to ORS New evidence in support</td>
</tr>
<tr>
<td>Zinc</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
2.4 References


38. Freedman SB, Steiner MJ, Chan KJ – Oral Ondansetron administered in emergency

2.5 Publications

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

2. Bruzzese E, Lo Vecchio A, Guarino A.
   Hospital management of children with acute gastroenteritis.

   Lindo E. The management of acute diarrhea in children in developed and developing areas:
   from evidence base to clinical practice.

A similar methodology has been used to produce the evidence-based guidelines developed by the
Italian Society of Pediatric Infectious Diseases – SITIP for the prevention, diagnosis and treatment
of Tuberculosis in pediatric age. The document is currently under revision by the World Health
Organization and cannot be reported in this thesis.

The final document will be available at the website: http://www.sitip.org with the following
reference:

4. Coordinators: Susanna Esposito and Alberto Villani
   Stearing Committee: Elena Chiappini, Maurizio de Martino, Luisa Galli, Alfredo Guarino, Laura
   Lancella, Andrea Lo Vecchio, Nicola Principi.
   Multidisciplinary panel: F Bernardi, E Bertazzoni Minelli, F Blasi, M Bocchino, S Bosis, E
   Castagnola, E Chiappini, D Ciofi, D Cirillo, L Codecasa, M de Martino, A Di Comite, G Di Mauro, S
   Esposito, M Faccini, F Festini, C Gabiano, L Galli, S Garazzino, A Guarino, L Lancella, G Losurdo, A
   Lo Vecchio, G Marseglia, A Mattelli, G Migliori, C Montagnani, A Pasinato, N Principi, C Russo,
   F Scaglione, E Scala, M Stronati, M Tadolini, E Tortoli, P Tomà, A Villani.
   Prevention, diagnosis and treatment of Tuberculosis in pediatric age.
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

*Alfredo Guarino (Coordinator), †Shai Ashkenazi, ‡Dominique Gendrel, ‡Andrea Lo Vecchio, †Reuman Shamir, and ‡Hania Szajewska

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.

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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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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 hypotonic 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. Antiviral therapy may reduce the duration and severity of diarrhea. Effective interventions include administration of specific probiotics such as *Lactobacillus* GG or *Saccharomyces boulardii*, diecortic or nocardophil. 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 outpatient setting. Enteral rehydration is superior to intravenous rehydration. Ultrapureed 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

(JPGN 2014;59: 132–152)

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 electrolyte 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>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Strong evidence from ≥1 systematic review(s) of well-designed RCTs</td>
</tr>
<tr>
<td>II</td>
<td>Strong evidence from ≥1 properly designed RCT(s) of appropriate size</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from well-designed trials without randomization, single group pre–post, cohort, time series, or matched case–control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from well-designed trials, non-experimental studies from &gt;1 center or research group</td>
</tr>
<tr>
<td>Va</td>
<td>Opinion of respected authorities</td>
</tr>
<tr>
<td>Vb</td>
<td>Clinical evidence, descriptive studies, or reports of expert committees</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Supported by level I evidence, highly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Supported by level II evidence, recommended</td>
</tr>
<tr>
<td>C</td>
<td>Supported by level III evidence, recommended</td>
</tr>
<tr>
<td>D</td>
<td>Supported by level IV and level V evidence; the consensus route would have to be adopted</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality</td>
<td>Further research is unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate quality</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low quality</td>
<td>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</td>
</tr>
<tr>
<td>Very low quality</td>
<td>Any estimate of effect is extremely uncertain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>When the desirable effects of an intervention clearly outweigh the undesirable effects, or they clearly do not</td>
</tr>
<tr>
<td>Weak</td>
<td>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)</td>
</tr>
</tbody>
</table>

with a more severe pattern of diarrhea, mainly in case of infection with specific genotypes (GI4 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 diarreheic 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 infection 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 rare in children returning from tropical countries.

5. RISK FACTORS FOR SEVERE AND/OR PERSISTENT DISEASE


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, enteraggregative 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 noroviruses 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). Infection 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 diarrheas in developing countries (III, C) (weak recommendation, low-quality evidence).

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

Children with immunodeficiency, undergoing 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 diarrheas 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/ A378).

Highly immunosuppressed patients failed to eliminate norovirus and had a higher risk of developing persistent or chronic diarrhea (48). Similarly, prolonged antigenemia during rotaviral infection was reported in stem cell transplant recipients (49). A retrospective study on >6500 children with rotaviral or noroviral 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 systemic 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). Reznick alopecia sebacea, 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 (36). 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 increased 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 (76,66,67). 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).
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, D) (weak recommendation, low-quality evidence).

Little is known about the severity of diarrhea and 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 impractical, 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).
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 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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>Normal</td>
<td>Thirsty, restless or lethargic but irritable when touched</td>
<td>Drowsy, limp, cold or sweaty and comatose</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Slightly sunken</td>
<td>Extremely sunken</td>
</tr>
<tr>
<td>Mucous membranes (tongue)</td>
<td>Moist</td>
<td>Sticky</td>
<td>Dry</td>
</tr>
<tr>
<td>Tears</td>
<td>Tears</td>
<td>Decreased tears</td>
<td>Absent tears</td>
</tr>
</tbody>
</table>

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.

**TABLE 4. Modified Vesikari score**

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1–96</th>
<th>97–120</th>
<th>≥121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea duration, h</td>
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<tr>
<td>Maximum number of diarrheal stools per 24-h period (in the course of the disease)</td>
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<tr>
<td>Vomiting duration, h</td>
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<tr>
<td>Maximum number of episodes per 24-h period (in the course of the disease)</td>
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<tr>
<td>Maximum recorded fever, °C</td>
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<td>37.1–38.4</td>
<td>38.5–38.9</td>
<td>≥39.0</td>
</tr>
<tr>
<td>Future health care visit</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>None</td>
<td>IV rehydration</td>
<td>Hospitalization</td>
<td>Emergency department</td>
</tr>
</tbody>
</table>

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 diarreal 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 diarreal episodes with small amounts of stool (25, 96), bloody stools, high fever, and abdominal pain (96) is more likely to be associated with 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 (77), 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) (II, 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 (Vb, D) (strong recommendation, low-quality evidence).
- In all children starting IV therapy, and during therapy, because hyper- or hypotension 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 hypotension, 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 and from systematic reviews. The regimens were similar in all trials, and a total volume of up 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; 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 its efficacy is comparable with IV fluids. It has been reported also in children with severe dehydration. Selected clinical conditions may, however, require IV rehydration. The following recommendations derive from expert consensus opinion and are similar to recommendations in other guidelines.

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·kg⁻¹·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 hypokalemia (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·kg⁻¹·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>
<thead>
<tr>
<th>Table 5. Holliday–Segar method to calculate maintenance fluid</th>
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<tbody>
<tr>
<td>Child’s weight</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>1–10 kg</td>
</tr>
<tr>
<td>10–20 kg</td>
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<tr>
<td>&gt;20 kg</td>
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</table>
Given this scenario, various scientific societies recommend a rapid IV infusion of approximately 20 mL·kg⁻¹·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·kg⁻¹·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 ≥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 hypotension and it 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 hypotension (79,117), and in a survey of pediatrics working in EDs in Canada and the United States, 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 hypotension 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 isotonic at admission developed mild hypotension 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·L⁻¹·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·L⁻¹·h⁻¹ (138). A more recent retrospective study confirmed the efficacy 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 reduces 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 rehydration with lactose-free formula (III, C) (weak recommendation, very low-quality evidence).

Lactose-free formulas can be considered in the management of AGE in hospitalized children aged <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 infant 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 aged <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 food products, 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 hydration 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 racemecotril (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 racemecotril showed a reduction in hospital costs related to an AGE event of approximately US$ 380 compared with ORS. The amount spared is related to primary care consultation 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 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 randomized 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 osmolality 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 probiotics (B. longum, L. casei, and S. cerevisiae) (152), glucose polymers (153) (154), 1-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 hypertonic ORS with a regular hypertonic 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 breastfeeding 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.

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, 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, cow’s milk-based 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).

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 98.09).
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/Formula, 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 (VIb, 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 (90% 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 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).


#### 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

Disodium

Disodium 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 (II, C) (weak recommendation, very low-quality evidence).

Only 1 trial (not identified in the 2008 edition of the ESPGHAN/ESPDID 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**

**Rocaccadotril**

Rocaccadotril 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 rocaccadotril 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, racccadotril significantly reduced the duration of diarrhea. Almost twice as many patients recovered at any time in the racccadotril group versus the placebo group (P = 0.001). There were no interactions between treatment and dehydration, rotavirus infection, type of study (inpatient or outpatient), or country. In the studies of inpatients, the ratio of mean stool output racccadotril/placebo was reduced (P < 0.001). In outpatient studies, the number of diarrheal stools was lower in the racccadotril 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 racccadotril 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 racccadotril in 2 studies. Also, the need for IV therapy was lower in the racccadotril 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 (II, 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% (9 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 where 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 NCT01199887).

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 provides recommended guidelines 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 Symbiotics

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

Symbiotics were not addressed in the previous ESPGHAN/ESPID guidelines owing to lack of data. Three RCTs evaluated the efficacy of symbiotics for the management of AGE. The first RCT compared the efficacy of a combination of 5 probiotic strains (*Streptococcus 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 symbiotic 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 symbiotic group than in the placebo group. Moreover, fewer additional medications (antipyretics, antiemetics, antibiotics) were administered in the symbiotic 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 × 10⁹ CFU, and 625 mg fructooligosaccharide for 5 days was evaluated. Administration of the symbiotic mixture in addition to conventional rehydration therapy compared with rehydration therapy 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 symbiotic combination (*L. paracasei* B21060 plus ambarinogalactan and xilooligosaccharides) also appeared to be beneficial. Resolution of diarrhea at 72 hours was significantly more frequent in children who received the symbiotic combination than in the placebo group (P = 0.005). Moreover, children in the symbiotic 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 symbiotic group.

9.3.7 Prebiotics

The use of prebiotics in 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)

<table>
<thead>
<tr>
<th>Strain(s)</th>
<th>Quality of evidence</th>
<th>Recommendation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics with a positive recommendation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGG</td>
<td>Low</td>
<td>Strong</td>
<td>≥10^10 CFU/day (typically 5–7 days)</td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em></td>
<td>Low</td>
<td>Strong</td>
<td>250–750 mg/day (typically 5–7 days)</td>
</tr>
<tr>
<td><em>Lactobacillus acidophilus</em></td>
<td>Very low</td>
<td>Weak</td>
<td>10^4–4 x 10^5 (typically 5–7 days)</td>
</tr>
<tr>
<td>Heat-killed <em>Lactobacillus acidophilus</em> LB*</td>
<td>Very low</td>
<td>Weak</td>
<td>Minimum 5 doses of 10^10 CFU for 48 h; maximum 9 doses of 10^10 CFU for 4.5 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strain(s)</th>
<th>Quality of evidence</th>
<th>Recommendation</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics with a negative recommendation</td>
<td></td>
<td></td>
<td>Safety issues (a possible recipient of the vancomycin-resistance genes)</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em> (SF68 strain)</td>
<td>Low</td>
<td>Strong</td>
<td>Safety issues (a possible recipient of the vancomycin-resistance genes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strain(s)</th>
<th>Quality of evidence</th>
<th>Reason for a lack of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em> Nissle 1917</td>
<td>Very low</td>
<td>Methodological issues</td>
</tr>
<tr>
<td><em>Lactic acidophilus</em></td>
<td>Very low</td>
<td>No strain identification</td>
</tr>
<tr>
<td><em>Lactic acidophilus</em></td>
<td>Moderate</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bacillus velezensis</em></td>
<td>Moderate</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Lactic acidophilus</em></td>
<td>Moderate</td>
<td>Only 1 RCT available; no strain identification</td>
</tr>
<tr>
<td><em>Lactic acidophilus</em></td>
<td>Low</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bifidobacterium longum</em></td>
<td>Very low</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em></td>
<td>Very low</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bifidobacterium bifidum</em></td>
<td>Very low</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em>, <em>Bifidobacterium</em></td>
<td>No data</td>
<td>Lack of data</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em>, <em>Bifidobacterium</em></td>
<td>Very low</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em>, <em>Bifidobacterium</em></td>
<td>Very low</td>
<td>Only 1 RCT available</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em>, <em>Bifidobacterium</em></td>
<td>Very low</td>
<td>No strain identification</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em>, <em>Bifidobacterium</em></td>
<td>Very low</td>
<td>No strain identification</td>
</tr>
</tbody>
</table>

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 etiologic 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 one of the 3 second-line antibodies (ampicillin, azithromycin, 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 findings, 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>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication for antibiotic therapy</th>
<th>Drug of choice(^a)</th>
<th>Alternative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shigella spp</td>
<td>Proven or suspected shigellosis</td>
<td>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)(^b)</td>
<td>Ceftriaxone (8 mg · kg(^{-1}) · day(^{-1})); ciprofloxacin(^1) PO (20-30 mg · kg(^{-1}) · day(^{-1})). For a known susceptible strain: TMP/SMX(^2) (8 mg · kg(^{-1}) · day(^{-1}) of TMP) or ampicillin (100 mg · kg(^{-1}) · day(^{-1})). Nalidixic acid (55 mg · kg(^{-1}) · day(^{-1}))</td>
</tr>
<tr>
<td>Salmonella spp (nontyphoidal)</td>
<td>Antibiotic therapy is indicated only in high-risk children to reduce the risk of bacteremia and extraintestinal focal infections</td>
<td>Ceftriaxone (50-100 mg · kg(^{-1}) · day(^{-1}))</td>
<td>Azithromycin (10 mg · kg(^{-1}) · day(^{-1})); ciprofloxacin(^1) PO (20-30 mg · kg(^{-1}) · day(^{-1})); for a known susceptible strain, TMP/SMX(^1) (8 mg · kg(^{-1}) · day(^{-1}) of TMP)</td>
</tr>
<tr>
<td>Campylobacter spp</td>
<td>Antibiotic therapy is recommended mainly for the dysenteric Campylobacter gastroenteritis and most efficacious when started within 3 days after onset of the disease</td>
<td>Azithromycin (10 mg · kg(^{-1}) · day(^{-1}) for 3 days, or a single dose of 30 mg/kg)</td>
<td>Doxycycline (&gt;8 years) or ciprofloxacin (&gt;17 years), when susceptible</td>
</tr>
<tr>
<td>Shiga toxin-producing Escherichia coli</td>
<td>Antibiotic therapy is not recommended</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Enterotoxigenic;</td>
<td>Antibiotic therapy is recommended, mainly for traveler’s diarrhea</td>
<td>Azithromycin (10 mg · kg(^{-1}) · day(^{-1}) for 3 days)</td>
<td>Ceftriaxone (8 mg · kg(^{-1}) · day(^{-1}) for 5 days); TMP/SMX(^1) (8 mg · kg(^{-1}) · day(^{-1}) of TMP); ciprofloxacin(^1) PO (20-30 mg · kg(^{-1}) · day(^{-1})); rifaximin (&gt;12 years, 600 mg/day, for 3 days)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Antibiotic therapy is recommended for confirmed or suspected case by travel history</td>
<td>Azithromycin (10 mg · kg(^{-1}) · day(^{-1}) for 3 days, or a single 20 mg/kg dose)</td>
<td>Doxycycline (&gt;8 years), Ciprofloxacin (&gt;17 years), or TMP/SMX(^1) (when susceptible)</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Antibiotic therapy is recommended for moderate and severe cases</td>
<td>Metronidazole (30 mg · kg(^{-1}) · day(^{-1}) for 10 days)</td>
<td>Vancomycin PO (40 mg · kg(^{-1}) · day(^{-1}))</td>
</tr>
</tbody>
</table>

\(^a\) Depends on local antibiotic susceptibility profile, which should be monitored.

\(^1\) TMP/SMX, trimethoprim-sulfamethoxazole.

\(^2\) 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.
to be more effective than either ceftriaxone 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 (i.e., in an outbreak setting), these agents are the recommended first-line treatment. Oral fluoroquinolones can be used in children age <17 years when no 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, anatomic 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 (I, 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-uremic 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 enter-aggregative *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·kg⁻¹·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. Alternatively, 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 (enterohemorrhagie *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 Enteral Pathogens or Involvement of Extrainestinal Organs

Antibiotic therapy is recommended for the rare but severe extraintestinal infections caused by 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 should be treated with metronidazole, nitazoxamide, albendazole, or tinidazole (III, C) (weak recommendation, low-quality evidence).

Cryptosporidiosis should be treated mainly in immuno-compromised children with nitazoxamide (III, C) (strong recommendation, low-quality evidence).

Amoebic 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 polyjparasitism. A recent trial in adults with *Giardia* mono-infection showed equivalence of the 2 drugs in terms of parasitological cure and improving symptoms (210). Tinidazole (single dose) had similar results; nitazoxamide 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). Nitazoxamide 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 immu-
nocompromised 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 treat-
ment. Consistent evidence demonstrated that oral adminis-
tration of immunoglobulin (300 mg/ kg) may be benefical 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 immunoglobulin Y (IgY) produced from
poultry eggs were found to be strongly reactive to several
viral 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
an 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 immuno-
compromised hosts (220); however, the most appropriate
treatment of isolated cytomegalovirus enterocolitis in immunocom-
petent 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 recom-
mandation, low-quality evidence).

One single-blinded trial (n = 75) conducted in Bolivia evalu-
ated the effectiveness of oral or systemic rehydration versus the
same intervention plus nitazoxanide or plus a probiotic preparation (L.
acidophilus, B. longum, and S. boullardii) 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 ESPGAN/ESPID recommendations
on the management of acute gastroenteritis can be found at

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Hospital management of children with acute gastroenteritis

Eugenia Bruzzese, Andrea Lo Vecchio, and Alfredo Guarino

**Purpose of review**
Acute gastroenteritis (AGE) is a major cause of ED visits, hospitalizations, and prescription of investigations, drugs, and changes in diet. Several guidelines on management have been produced.

**Recent findings**
There is new information on different rehydration protocols, use of antiemetics, and antidiarreal drugs that could reduce the burden of AGE. The need of intravenous (i.v.) rehydration is the main cause of hospital admission yet standardized rehydration schemes are not available. Rehydration therapy through nasogastric tube is better than i.v. rehydration, in children with moderate-severe dehydration. Ultrapid rehydration has been proposed by enteric or i.v. route to reduce the time in hospital and costs. However, reduced rehydration times are associated with high readmission rates and side effects. Antiemetics may reduce the need of i.v. rehydration because of vomiting and the number of hospital admissions. However, the main antiemetic, ondansetron, has been loaded with a warning for potentially severe side effects. Selected anti-diarrheal drugs could reduce the length of stay, but data on their use in inpatients are still not conclusive.

**Summary**
Inappropriate medical interventions are still common in the hospital setting and have a high impact on costs. A validated management is still needed in inpatients.

**Keywords**
acute diarrhea, acute gastroenteritis, hospital, rehydration

**INTRODUCTION**
Acute gastroenteritis (AGE) has a high spectrum of severity whose hallmark is dehydration, which requires replacement of fluids usually through oral route [1]. The effectiveness of oral rehydration solution (ORS) in children with mild-to-moderate dehydration has been demonstrated by a Cochrane meta-analysis showing no clinical differences between oral and parenteral rehydration therapy in children with AGE [2]. However, failure of oral rehydration is the main indication to hospital admission and to receive enteral or intravenous rehydration therapy (IVT) [3,4]. However, the majority of articles on AGE management do not specifically address the problem of inpatients management and the recommendations for intravenous (i.v.) rehydration are poorly standardized. However, the National Institute for Health and Clinical Excellence [5] and more recently the Cincinnati Children’s Hospital [6*], specifically provided i.v. rehydration protocols, indications to laboratory investigations and criteria for hospital discharge.

The purpose of this review is to discuss when and how a child with acute diarrhea should receive i.v. rehydration, the indications to enteral rehydration and laboratory tests and finally to summarize recent evidence for active treatment of AGE in the inpatient setting.

**INDICATIONS TO HOSPITAL ADMISSION FOR ACUTE GASTROENTERITIS**
Indications to hospital admission for acute gastroenteritis are based on opinion of experts. Hospital admission is recommended in case of severe dehydration, shock, failure of oral rehydration therapy...
KEY POINTS

- Reliable data are available mostly for outpatients and indications for inpatients are mostly based on opinion and indirect data.
- Standard indications for nasogastric/i.v. rehydration and their schemes are not available.
- Antiemetics are largely used and effective, but there are issues on their safety.
- Drugs used in outpatients could be used in inpatients also with good results, but the ideal drug for diarrhea is still to be identified.

Gastrointestinal infections

INDICATIONS TO LABORATORY AND MICROBIOLOGICAL INVESTIGATIONS

AGE does not usually require stool microbiological investigations. Most children have a viral cause and in addition bacterial or protozoal agents generally do not require antimicrobial treatment. Stool cultures should be considered in case of persistent diarrhea, when antimicrobial treatment is considered (e.g. in immune-compromised children, in septic or toxic children or children with dysentery), in case of an outbreak or if the child has recently been abroad.

Electrolyte abnormalities may develop, although usually they are not severe. Hypernatremia and hyponatremia may occur, although isonatremic dehydration is the most common form. Selected children may have hypoglycemia and some may present metabolic acidosis, but their incidence is low. Furthermore, the accuracy of available tests in detecting severity of dehydration is not established. The laboratory test that best correlates with dehydration is serum bicarbonate [10]. Blood tests are not routinely needed, but serum potassium, sodium, urea and creatinine, and serum bicarbonate should be considered for children severely

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Table 1. Indications to visit or emergency/hospital admission according to available guidelines

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<tr>
<td>Age below 2 months</td>
<td>+</td>
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<tr>
<td>Persistent fever after 24 h of ORT</td>
<td>+</td>
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<tr>
<td>The child refuses to drink</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Reduction of urinary output</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>High volume diarrhea</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Diarrhea persisting more than 1 week</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Persistent vomiting that does not allow oral rehydration</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Vomiting associated with abdominal distention and pain</td>
<td>+</td>
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<tr>
<td>Mucous or bloody diarrhea</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Severe stomachache</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Lethargic, restless or irritable</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Severe underlying diseases (i.e. diabetes and renal failure)</td>
<td>+</td>
<td>+</td>
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| Social or logistical concerns | +               | +                   | +                      |                        |

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<tbody>
<tr>
<td>Severe dehydration and/or shock</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Oral rehydration failure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Intractable vomiting</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neurological abnormalities (lethargy, seizures, etc)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Suspected surgical conditions</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Social or logistical concerns</td>
<td>+</td>
<td>+</td>
<td>+</td>
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*All the indications to medical consultation represent a criteria for ED visit if physician is not available within few hours [7].
*Indications to hospital admission are extrapolated from criteria for intravenous rehydration [8*].
dehydrated or in whom i.v. rehydration is required. However, in the absence of risk-benefit indications, ordering laboratory tests based on clinical judgment may be superior to routine screening [6**]. Despite this, a recent survey showed that 40–60% of enrolled physicians require laboratory tests in moderately dehydrated patients [11*].

**REHYDRATION THERAPY**

Rehydration may be provided through oral, enteral (through nasogastric tube; NGT), and i.v. route according to the severity of dehydration and the conditions of the child. In the hospital setting, the last two options are typically considered.

**Rehydration through nasogastric tube**

A Cochrane review compared the efficacy of IVT in 17 trials with oral or nasogastric rehydration [2], in eight of 17 trials, rehydration was given through NGT alone or in combination with ORT. There were no differences in the rehydration failure, incidence of hypernatremia, hypernatremia, mean duration of diarrhea, weight gain, or total fluid intake in children on ORT or IVT. Children on ORT had a significantly shorter stay in hospital and a lower risk of phlebitis [2]. A meta-analysis showed that NGT rehydration is associated with reduced risk of electrolyte imbalances, cerebral edema, phlebitis compared with i.v. rehydration. Rehydration through NGT is a valid alternative to IVT with equal efficacy, less adverse events and reduces the length of hospital stay [12].

Current guidelines concluded that rehydration should be provided through NGT if children are unable to drink it or if they have persistent vomit. The American Academy of Pediatrics recommends rapid (over 4 h) NGT rehydration for treatment of children with moderate dehydration. This regimen offers several benefits including a shorter stay in the hospital and less disruption of the family routine compared with the standard regimen. A prospective, randomized, clinical trial compared two different regimens of nasogastric rehydration: the standard nasogastric regimen (SNR) (replace fluids over 24 h) and the rapid nasogastric regimen (RNR) (100 ml/kg of rehydration solution administered over 4 h) [13*]. The results showed no significant difference in the primary treatment failure defined as an additional loss of more than 2% of weight at any time during the rehydration period. Furthermore, no differences in the secondary treatment failures defined as inability to tolerate NGT, persistent vomiting, need of i.v. rehydration, persistent signs of moderate dehydration, need of nasogastric fluids beyond 24 h, were observed between the two groups at 4–6 h after beginning of rehydration therapy. At 24 h and 7 days after the admission, a higher proportion of secondary treatment failures in the RNR group compared with the SNR group was observed.

Despite the evidence of safety and efficacy, NGT rehydration regimen continues to be poorly applied in clinical practice, perhaps because placing a NGT is considered more invasive than IVT. These concerns need to be balanced against the i.v. complications such as phlebitis or cellulitis.

**Intravenous rehydration**

The indications to IVT generally overlap the indications to hospital admission. Guidelines recommend i.v. rehydration in case of severe dehydration and/or in case of oral rehydration failure. The recent evidence-based guidelines from Cincinnati Children’s Hospital [6**] recommend i.v. therapy, if there is a severe dehydration or if it is impossible to replace the estimated deficit fluids using oral solution alone.

Intravenous rehydration consists in the administration of an isotonic crystalloid solution without dextrose as an i.v. bolus of 20 ml/kg followed by a continuous infusion of dextrose – containing crystalloid solution if prolonged hydration is required. Intravenous rehydration should be started with isotonic fluid (normal saline) because this is more effective in reducing the risk of hyponatremia than hypotonic fluids (half normal saline with 5% dextrose) [14]. Isotonic Ringer lactate is associated with a better outcome from shock compared with hypotonic fluids in children with severe malnutrition and hypovolemia [15]. The Cincinnati Children’s Hospital guidelines [6**] recommend to start IVT with a bolus of 20 ml/kg of normal saline over 30–60 min followed by a maintenance volume of half normal saline with 5% dextrose to replace losses and maintain hydration. Despite the lack of evidence of efficacy, in the last years a rapid rehydration scheme (40–60 ml/kg normal saline bolus over 60 min) has been gradually incorporated into clinical practice with the aim to obtain a reduction of symptoms, an improvement of appetite, and a reduction of hospital stay and of global costs of AGE. A survey of North American physicians, specialized in pediatric emergency, found that several regimens are used [16**]. In a recent clinical trial comparing two different i.v. schemes, the tolerance to the administration of 50 ml/kg in 1 h was similar to that of 50 ml/kg in 3 h, but it was associated to earlier discharge from emergency department (ED) [17]. A recent trial comparing the effect of boluses of 20–40 ml/kg of 5% albumin solution or 0.9% saline solution or no bolus in critically ill African children,
showed that both bolus-fluid resuscitation, compared with no bolus regimen, increased the absolute risk of death at 48 h by 3.9%. These data, although obtained in clinical conditions other than AGE, suggest that there may be severe risks associated to rapid rehydration regimens [18**]. In order to evaluate the efficacy of rapid rehydration for AGE-induced dehydration, a randomized blinded comparative trial was conducted in children in whom oral rehydration failed and i.v. rehydration was required [19**]. Children randomly received a 20 mL/kg (standard) or 60 mL/kg (rapid) of 0.9% saline infusion over 60 min followed by 5% dextrose in 0.9% saline at maintenance rate. Clinical dehydration scores, vital signs, and adverse events were recorded every 30 min for a total of 4 h. No difference in the percentage of children rehydrated after 2 h was observed between the two groups (36% in rapid rehydration vs. 39% in standard rehydration group). There was no difference in the rates of prolonged treatment, mean dehydration scores, repeat visits to emergency, adequate oral intake. However, the median time to discharge was significantly longer in the rapid compared with the standard group (6.3 vs. 5.0 h; P = 0.03) and children receiving rapid i.v. rehydration were more commonly admitted to the hospital. The authors concluded that none of the outcomes support the use of rapid i.v. rehydration and that there was a trend toward worse outcomes in these children. This data strongly indicate that the routine use of i.v. rapid rehydration should be prescribed cautiously.

**PHARMACOLOGIC TREATMENT**

Only few of the many drugs proposed for AGE have proof of efficacy in preventing complications and in reducing hospital admission, duration of symptoms and the length of stay in hospital setting (Table 2).

**Antiemetics**

Vomiting is probably the main indirect cause of hospital admission. However, the therapy for vomiting remains controversial. None of the currently available guidelines suggests a routine use of antiemetics in children with AGE [3–5,6**,7,8*], but emerging evidence indicates that selected antiemetics may help in oral rehydration delivery, and reduce i.v. rehydration and hospital admissions.

The use of ondansetron, a selective (5-HT3) serotonin antagonist, is progressively increasing [20*] to the point that American Pediatric Emergency Medicine Physicians indicated ondansetron as the drug of choice in vomiting patients with AGE [16**].

A recent systematic review, including seven trials and more than 1000 patients, provided

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**Table 2. Effects by anti diarrheal drugs in hospital setting and their level of evidence**

<table>
<thead>
<tr>
<th>Antidiarrheal drug</th>
<th>Dose</th>
<th>Effect on duration of hospitalization</th>
<th>Other outcome measures</th>
<th>Best level of evidence available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>10^{10} CFU per day</td>
<td>Reduction of LOS for rotavirus diarrhea; Trend toward reduction to LOS, but not conclusive evidence for other etiologies</td>
<td>Duration of diarrhea; Risk of prolonged diarrhea; Duration of hospitalization</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>rhamnosus GG (LGG)</td>
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<td></td>
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</tr>
<tr>
<td>S. boulardii</td>
<td>200–500 mg per day (about 4–10 × 10^{5} CFU)</td>
<td>Reduction of LOS of about 1 day</td>
<td>Duration of diarrhea; Risk of prolonged diarrhea; Duration of hospitalization</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Few studies consider LOS)</td>
</tr>
<tr>
<td>Racecadotril</td>
<td>1 1.5 mg/kg TID</td>
<td>Not assessed</td>
<td>Stool output; Duration of diarrhea</td>
<td>Systematic review; Meta-analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>10 mg &lt;6 months of age; 20 mg &gt;6 months of age</td>
<td>Not assessed</td>
<td>Duration of diarrhea; Stool output; Risk of hospitalization; Death</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smectite</td>
<td>3 g &lt;1 year of age; 6 g 1–2 years of age; 6–12 g &gt;2 years of age</td>
<td>Not assessed</td>
<td>Duration of diarrhea; Risk of prolonged diarrhea; Number of stools</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral administration of immunoglobulins</td>
<td>200–300 mg/kg per day</td>
<td>Reduction of LOS for rotavirus diarrhea in at risk children or in severe conditions</td>
<td>Intake of oral fluids; Duration of intravenous rehydration; Resolution of diarrheal symptoms</td>
<td>Controlled studies</td>
</tr>
</tbody>
</table>

*No clear distinction between in- and outpatients effect size.

*Length of stay.
evidence in support of ondansetron as adjunct therapy in case of mild-moderate dehydration [21**].

A single oral dose (0.15–0.3 mg/kg) of ondansetron controlled vomiting and reduced hospitalization rates [risk ratio (RR) 0.40, 95% CI 0.19–0.83, \( P = 0.01 \)] and i.v. fluids need (RR 0.57, 95% CI 0.42–0.76, \( P = 0.0002, \text{NNT} = 6 \)) when administered in EDs [21**]. This intervention may be highly cost-effective [22].

In a 5-year retrospective study, the increased use of ondansetron (from 1 to 18%) was associated with a reduction of i.v. rehydration (from 26 to 14%, \( P < 0.001 \)), length of stay in ED (8.6 ± 3.4 to 5.9 ± 2.8 h, \( P = 0.03 \)) and return visits (18–13% \( P = 0.008 \)) [20*].

Major concerns on antiemetics prescription have been historically related to the potential side effects. A Cochrane review only reported few cases of increased diarrhea secondary to ondansetron administration [21**]. Nevertheless, in September 2011, the US Food and Drug Administration (FDA) released a warning on the use of ondansetron in patients with underlying heart conditions, such as congenital long QT syndrome, heart failure, and bradyarrhythmias [23]. This was based on case reports of QT prolongation after ondansetron administration in adults [24] and children [25]. However, in addition to heart conditions, the FDA extended the warning to patients predisposed to hypokalemia and hypomagnesemia, or taking medications that may lead to QT prolongation. Abnormalities in electrolyte serum levels may be frequent in AGE, which opens a burning question on a routine use of ondansetron to prevent the need of i.v. rehydration and hospitalization in the light of some (low) risk of (potentially severe) side effects.

Antiemetic drugs alternative to ondansetron are limited; domperidone is a widely used drug with little evidence of efficacy [26]. A randomized controlled trial assessing the efficacy of ondansetron and domperidone compared with placebo in children admitted to EDs for AGE is currently ongoing in Italy [27*].

A recent trial in Qatar showed no difference between ondansetron and metoclopramide in cessation of vomiting, length of stay, and side effects [28*]. On the basis of these results, it was suggested that metoclopramide could represent an effective and cost-sparing alternative to ondansetron for persistent vomiting in poor countries. Considering the severe side effects reported for metoclopramide, this proposal raises concerns in terms of safety, mainly in developing areas where surveillance and accurate follow-up are limited.

Indications are, therefore, strongly needed on the use of antiemetics in AGE.

### Antidiarrheal drugs

The simple replacement of lost fluids does not shorten the course of diarrhea and different approaches have been proposed to reduce duration and severity of diarrhea in hospitalized children, such as antimitoty/anitiperistaltic drugs, antisecretory, absorbents, and antimicrobial treatments.

### Probiotics

These are recognized as first-line therapy for AGE in adjunct to rehydration [29], based on a demonstrated effect in reducing the duration of diarrhea by about 24 h, the risk of diarrhea lasting at least 4 days and the stool frequency on day 2 [30*]. An analysis on hospitalized children also showed a significant effect of probiotics on duration of diarrhea (mean difference −20.90 h 95% CI −31.44 to −10.35) [30*].

As the beneficial effects of probiotics are strain related, pooling data on different strains is inappropriate.

*Lactobacillus rhamnosus* GG [LGG] and *Saccharomyces boulardii* are the two strains, with consistent evidence of efficacy. LGG is the recommended treatment in evidence-based guidelines [3,6**]. It also reduced the duration of hospitalization in previous meta-analysis [31].

Two recent double-blind RCTs, were conducted on *S. boulardii* in children hospitalized in low-income areas.

The first was carried out in two Brazilian hospitals and showed a reduction of diarrhea duration within 72 h from its onset. This reduction was significant in children with rotavirus infection (RR 0.45, 95% CI 0.28–0.74), but not in nonrotaviral diarrheal episodes [32*].

The second study, performed on a small Bolivian population with rotaviral infection, compared the effect of *S. boulardii* and a mix of probiotics containing lactobacilli, bifidobacteria and *S. boulardii* with placebo. The authors reported a modest but significant effect of *S. boulardii* on the duration of diarrhea that was not observed with the combined probiotic product [33*]. A new strain (DSM 17938) of *Lactobacillus reuteri* was tested in 70 children hospitalized with mild-to-moderate diarrhea [34,35*]. L. *reuteri* reduced the duration of diarrhea (2.1±1.7 vs. 3.3±2.1 days, \( P < 0.03 \)) and the prevalence of children with diarrheal stools at day 2 (55 vs. 81%, \( P < 0.02 \)) and day 3 (46 vs. 73%, \( P < 0.03 \)).

Guidelines produced in developing countries do not recommend probiotics in children with AGE [36] and their administration is currently considered as a common violation to recommendations [37*].

This discrepancy between different geographic settings is essentially due to the limited evidence of...
efficacy available in developing areas wherein cause of diarrhea, availability of fluids/water and probably alimentary habits may limit probiotic efficacy.

**Raccaadotril**

Raccaadotril, an enkephalinase inhibitor, is not approved by US FDA and data comes from European countries and developing areas [38**]. In a recent meta-analysis including nine RCTs and more than 1300 inpatients and outpatients, raccaadotril was effective in reducing diarrhea duration and stool output. The effect was independent from dehydration, rotavirus positivity and country [39**].

A deterministic and probabilistic sensitivity analysis on the economic impact of raccaadotril showed a reduction in the hospital expenses related to AGE event by about £380 due to primary care consultation and secondary referral [40**].

**Other antidiarrheal drugs**

Zinc supplementation is recommended as universal treatment for acute diarrhea in childhood [3], based on several clinical trials and meta-analysis [41–43]. Efficacy is unclear in nonmaldnourished children [44**], but a clear efficacy has been shown in children severely malnourished [41].

Zinc-enriched ORS did not show similar efficacy in a recent trial in Indian inpatients [46**]. A randomized placebo-controlled trial assessing the efficacy of a 14-days oral zinc supplementation in US inpatients and outpatients children is currently ongoing at the Boston Children’s Hospital. The length of stay is the main outcome measure (clinicaltrials.gov NCT01198587).

Smectite is a natural clay with effects on permeability, cytokine production and electrolyte secretion, able to reduce duration of diarrhea and stool volumes.

A controlled trial, involving about 100 Indian children, showed a significant reduction of diarrhea duration of about 18h [47**].

A further option to be considered in severe and/or immunocompromised patients or in severe AGE episodes is oral administration of immunoglobulins [48,49]. This approach seems highly indicated for children in severe conditions with viral diarrhea. Oral administration of a hyperimmune immunoglobulin preparation produced from hens immunized against human rotavirus (anti HRV IgY, 500 mg x 4 per day) showed a significant effect on rotavirus excretion (P = 0.05), duration of diarrhea (P = 0.01), duration of i.v. rehydration (P = 0.03) and ORS needed (P = 0.004) [50**]. As almost all the patients (92%) in the trial had, together with the rotavirus infection, a second enteric noncholera pathogen, the authors speculated that the product may improve the clinical outcomes also in patients with mixed enteric infections.

Florescu et al. [51**] proposed the oral administration human immunoglobulins, for norovirus enteritis in a small population of patients that underwent bone marrow or solid organ transplantation or chemotherapy. A trend toward resolution of diarrhea and stool output was observed after 7 days from the onset of symptoms, although no benefits were found on the length of stay and hospital costs.

**Antibiotics**

Antibiotics are not routinely recommended in pediatric AGE [3] and they may increase costs, prolong diarrheal episodes, and contribute to spreading antibiotic resistance [52]. A quality care improvement approach with a multifaceted intervention led to a weak reduction of inappropriate antibiotic prescription in children with AGE in Kenya [53**].

In developing areas where antibiotics are largely used to manage AGE, antibiotic resistance is becoming a common problem [54,55**,56] and new molecules are being tested.

Vinh et al. [57**] recently tested the efficacy of a 3-day course of ciprofloxacin compared with the WHO standard treatment with ciprofloxacin for shigellosis in hospitalized children with no significant difference between the two antibiotics in terms of treatment failure (about 10%) and resolution of symptoms.

**CONCLUSION**

Several guidelines on the management of AGE in children are available, of good quality and similar in their indications [58**]. Their application should limit the high number of inappropriate interventions that are common in hospital settings and could significantly reduce hospital costs [59]. Children admitted to ED with mild-to-moderate dehydration often receive i.v. fluids and unnecessary laboratory tests. However, protocols to rehydrate children with AGE are needed. The rapid/ultrarapid rehydration schemes may be loaded with electrolyte imbalances and have no clear advantages compared with standard rehydration. The main advantage is an early discharge with the reduction of the ED overcrowding, however, children treated with rapid i.v. rehydration are often readmitted to the ED. Several studies support the use of antiemetics in ED to prevent hospitalization, but recently the FDA released a warning on the use of ondansetron in patients with underlying heart conditions and electrolyte disorders. Finally, although AGE is a self-limiting disease, several efforts are ongoing to find the ‘ideal drug’ for treatment of acute diarrhea.
Acknowledgements
None.

Conflicts of interest
The authors have no conflict of interest to be declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as 
- of special interest
- outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 93–94).


13. This is a survey comparing the management strategies for AGE of pediatric-trained and nonpediatric-trained emergency medicine physicians. It demonstrates that a large number of physicians frequently violate available guidelines. Although the article has several limitations due to the fact that the survey is not validated and is based on a ‘vignette’, its results are in keeping with other reports and the anonymous responses truly reflect what happens in clinical practice.


16. This randomized controlled trial showed no significant difference in rehydration efficacy between a rapid regimen (100 ml/kg over 4 h) and the standard regimen of nasogastric rehydration (replacement of fluids over 24 h). Interestingly, a significant proportion of subjects experienced treatment failure in the rapid rehydration group observed. The study has several limitations. It is not a double-blind study, the sample size has not been reached.

17. A recent, double-blinded randomized controlled trial comparing the efficacy of oral rehydration and metoclopramide in 167 children with AGE and suggesting a role of metoclopramide as cost-effective alternative to ondansetron in developing areas and other poor settings.


19. A recent, double-blinded randomized controlled trial comparing the efficacy of oral rehydration and metoclopramide in 167 children with AGE and suggesting a role of metoclopramide as cost-effective alternative to ondansetron in developing areas and other poor settings.

Gastrointestinal infections


A Cochrane meta-analysis on the use of probiotics as treatment for acute gastroenteritis. The authors report a significant effect of probiotics in reducing duration and frequency of diarrhoea and the risk of persistent diarrhoea. However, this lack of subgroup analysis makes those results difficult to be applied in the pediatric hospital setting.


An interventional-to-treatment pre-post-control analysis reported significant results of the intervention on duration of diarrhea, but when data were analyzed according to the presence of rotavirus, it was clear that a cumulative effect size was responsible for the efficacy of S. boydii on viral rotavirus infection.


This trial provides evidence in support of S. boydii obtained in rotavirus diarrhoea.


35. This RCT was performed on a small population of infants and demonstrated the efficacy of the new L. reuteri daughter strain in reducing duration and relapse of diarrhea. No recurrence has been found for the length of stay.


A cross-sectional study assessing the prescribing for acute gastroenteritis in major hospitals and pharmacies in a big Indian city. Any prescription but ORS and zinc, was considered to be inappropriate according to referral guidelines. Only a minority of prescriptions were made in compliance with recommendations.


A critical evaluation of therapeutic interventions with a worldwide perspective.


This is the first meta-analysis assessing the effect of raceacetol for acute diarrhoea. The authors included published and not published data, and performed an individual patient analysis introducing as outcome measure the percentage of patients with diarrhoea shorter than 2 days. Although there was no subgroup analysis for hospitalized patients, the stool output, a reliable outcome measure considered in hospitalized patients, showed a significant reduction. Some methodological issues related to the subgroup analysis, outcome measures and study selection, may limit these conclusions.


A recent cost-effectiveness analysis on the use of raceacetol in children with AGE. According to the authors raceacetol seems to be cost effective from a UK payer perspective, as it reduces costs by £380.


A recent single blind placebo-controlled trial on the use of zinc-enriched ORS in Italian children with AGE showing an effect of intervention in reducing diarrhoea duration.


A recent randomized open-label controlled trial on 177 Indian children with acute watery diarrhea. Zinc was associated with a reduction of diarrheal duration and prevention of protracted course of diarrhoea without any relevant side effect nor difficulty in drug administration.


A recent randomized placebo-controlled trial on 300 Indian children randomized to ORS or Zinc ORS, does not support the use of enriched oral solution and this setting.


A recent randomized open-label controlled trial on 117 Indian children with acute watery diarrhea. Smectide was associated with a reduction of diarrheal duration and prevention of protracted course of diarrhoea without any relevant side effect nor difficulty in drug administration.


In this article the authors reported the effects of hyperimmune immunoglobulin against a broad range of rotavirus serotypes on diarrheal outcomes in mice and in a population of children aged 3–14 months with acute rotavirus gastroenteritis. The results demonstrate a potential role of oral immunoglobulin as therapy of acute infectious enteritis in pediatric patients.


A matched case-control study on a small and heterogeneous population (24 patients) of adults and children (mean age 2 years) mainly the recipients of bone marrow or solid organ transplantion treated with a total dose of 200 mg/kg of human immunoglobulins administration through oral route eight times in 2 days.


A randomized quality improvement intervention multicenter study carried out in Kenya to reduce the inappropriate use of antibiotics in children hospitalized for AGE. The authors reported a substantial effect on antibiotic prescription also if the efficacy of the multifaceted intervention is not significant.


A recent controlled study analyzing the cause and resistance pattern of 600 cases of diarrhoea in a developing country. The authors reported a high prevalence of antibiotic resistance for the most frequent isolated pathogens.


A randomized controlled open-label trial comparing the effects of a new generation fluoroquinolone (gatifloxacin) vs. the standard treatment with ciprofloxacin in Vietnam, a Shigella endemic area with a high prevalence of antibiotic resistant bacterial strains.


A methodological evaluation of quality guidelines on AGE in children performed through the Appraisal of Guidelines for Research and Evaluation instrument. The assessment highlights the main strengths and limitations of single documents and shows an overall solid quality level with some limitation in stakeholder involvement and editorial independence.

The management of acute diarrhea in children in developed and developing areas: from evidence base to clinical practice

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¹University of Naples ‘Federico II’, Department of Pediatrics, Naples, Italy

Introduction: Acute diarrhea remains a major problem in children and is associated with substantial morbidity, mortality and costs. While vaccination against rotavirus could reduce the burden of the disease, the persistent impact of intestinal infections requires effective treatment in adjunct to oral rehydration solutions, to reduce the severity and duration of diarrhea. Several therapeutic options have been proposed for acute diarrhea, but proof of efficacy is available for few of them, including zinc, diosmectite, selected probiotics and racecadotril. However, at present there is no universal drug, and therapeutic efficacy has only been shown for selected drugs in selected settings, such as: outpatients/inpatients, developed/developing countries and viral/bacterial etiology.

Areas covered: This narrative review reports the opinions of experts from different countries of the world who have discussed strategies to improve the management of diarrhea.

Expert opinion: More data are needed to optimize the management of diarrhea and highlight the research priorities at a global level; such priorities include improved recommendations on oral rehydration solution composition, and the reevaluation of therapeutic options in the light of new trials. Therapeutic strategies need to be assessed in different settings, and pharmaco-economic analyses based on country-specific data are needed. Transfer to clinical practice should result from the implementation of guidelines tailored at a local level, with an eye on costs.

Keywords: acute diarrhea, children, diosmectite, gastroenteritis, pharmaco-economics, probiotics, racecadotril, rotavirus, zinc

1. Introduction

Acute diarrhea is very common in young children aged < 5 years and contributes to substantial mortality and morbidity [1]. Thanks to a program for the control of diarrheal disease, essentially promoted by the World Health Organization (WHO) and focused on the intense promotion of oral rehydration solution at the community level and the training of healthcare workers, diarrhea mortality rates dropped by 75% from 1980 to 2008 worldwide; but this is still unacceptably high and seems to have remained consistent for the last 5 years [2]. In developing regions, acute diarrhea still represents a leading cause of child mortality, second only to pneumonia [3,4]. While generally a mild, self-limiting disease in developed
Management of acute diarrhea in children

countries, gastroenteritis is a frequent cause of hospitalization and is associated with a substantial disease burden [1].

2. Burden of acute diarrhea

The severity of acute diarrhea is related to etiology, with rotavirus infection disproportionately implicated in severe cases that frequently require hospitalization [5]. Worldwide, up to 40% of children with diarrhea aged < 5 years are hospitalized with rotavirus [6]. While most of the associated disease burden is in developing countries as a reflection of demographics and underlying risk factors, the relative burden is comparable between developed and developing countries. In Europe, rotavirus infection accounts for > 50% of hospitalizations for gastroenteritis and about one-third of emergency department visits [7]. Similar trends extend to developing regions [8]. Not surprisingly, the economic burden of acute diarrhea is substantial, not only in management costs but also in indirect costs such as absence from work by parents or caregivers of sick children. In the USA, Canada and Europe, societal costs associated with rotavirus infection in children aged < 5 years have been estimated at > 50% of the total costs of care, with direct costs estimated at about one-third. Hospitalization accounts for most (78%) of the direct costs [9,10]. This high burden of societal costs is also evident in developing countries such as Vietnam [11].

The development of rotavirus vaccines is a priority, given this burden of disease. Two live, oral, attenuated rotavirus vaccines were licensed in 2006, a pentavalent bovine-human reassortant vaccine (Rotarix®) and a monovalent human rotavirus vaccine (Rotavac®). Both vaccines have demonstrated good safety and efficacy profiles in large clinical trials in industrialized countries and in Latin America [12,13]. Immunization against rotavirus is recommended in Europe and the USA [9,14]. While large-scale immunization is effective in reducing the severity of infections and hospital admissions in developing countries, the cost and the infrastructure hamper large-scale immunization programs, whereas reimbursement issues and parental acceptance are barriers to optimal implementation in rich countries [15].

3. Recommended management of gastroenteritis

The management of acute gastroenteritis aims at reducing the overall burden of this common disease in terms of incidence, morbidity and mortality worldwide.

The local epidemiology, impact of the illness and availability of adequate resources could modify recommendations and clinical approach in different settings. The WHO and UNICEF jointly produced documents essentially focused on children living in developing countries where diarrhea-related mortality is still common [16].

In Europe, evidence-based guidelines, jointly produced by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society of Pediatric Infectious Diseases (ESPGHAN/ESPID), provide a standard for the management of children with acute diarrhea [1]. This and other recently published evidence-based guidelines for children living in developed countries (UK, USA, Australia) focus on morbidity and socio-economic aspects [17-19].

Routine management of acute diarrhea should be based on clinical features. Microbiological examination is not helpful in the majority of cases and should be reserved for persistent diarrhea for which antibiotic treatment is potentially useful. However, compliance with the guidelines is far from optimal, and generally inappropriate medical interventions for acute gastroenteritis may increase the costs while prolonging the duration of the disease [20].

Oral rehydration solution (ORS) is recommended as first-line treatment for acute diarrhea and should be initiated as soon as possible after the onset of symptoms [1,16]. Oral rehydration solution is commonly used worldwide, also if the composition of the ORS is not yet standardized and different sodium concentrations are routinely used in different countries. So far, most trials have been conducted using the WHO standard ORS (90 mmol/liter Na+) or the ‘reduced osmolality’ ORS (75 mmol/liter Na+) in children in developing regions. Large systematic reviews showed that the so-called ‘reduced osmolality’ ORS was associated with fewer unscheduled intravenous fluid infusions, lower stool volume and less vomiting than the WHO standard ORS [16,21]. However, the ESPGHAN/ESPID guidelines have questioned the appropriateness of this formulation to the European setting and recommend the use of the so-called ESPHAGN solution, (or hypoosmolar solution, 60 mmol/liter Na+ concentration) for children of Europe [1]. ESPHAGN solution was effective, well tolerated and safe given the risk of cholera is very low in Europe [27]. Recently updated guidelines for the management of acute diarrhea in USA recommend hypoosmolar solutions containing 45 mmol/liter Na+ [19].

However, most data on ORS composition have been obtained from trials in children in developing countries, highlighting the need for trials with ORS formulations clinically appropriate for children in developed countries. Although a Cochrane meta-analysis [21], as well as the WHO documents [16], indicate the use of 75-mmol/liter solution, it should be noted that several trials included in those documents used hypoosmolar solution containing 60 mmol Na+, also in developing countries [22-24] and cholera areas [25]. The WHO clearly states that ORS solutions containing 60–90 mmol/liter of sodium are effective, and this reflects the indications from developing countries. It is well possible that high sodium composition is suboptimal in developed countries. The risk of cholera and hypotremia and also palatability are the major factors that influence the different approaches worldwide. Ideally, a universal ORS would be the best solution to increase its use, but the equilibrium between efficacy, safety, palatability and stability should be investigated in greater depth [28].
4. Options for active treatment of gastroenteritis

While ORS is essential for correcting or preventing dehydration, it does not reduce the severity or the duration of diarrhea, which raises the need for an active therapy. Clearly, it is important that such therapy be effective and well tolerated, especially as it is likely to be administered at home.

The ideal drug for gastroenteritis should have several features, which are summarized in Box 1. A drug with all those features does not exist, but selected commercially available drugs have a good profile, whereas many have not. The major problem for the vast majority of drugs proposed for gastroenteritis is the lack of evidence of efficacy. For some there is some additional worry. Anti-motility agents, such as loperamide, are not recommended for use in children because of the potential for fatal side effects [26].

Among a wide range of drugs proposed for gastroenteritis, evidence of efficacy is available only for zinc, racecadotril, diosmete and selected (very few) probiotic strains (Table 1).

4.1 Zinc

Zinc supplementation (at low doses) is recommended by both UNICEF and WHO as a universal treatment for acute diarrhea in childhood [27].

In the last 3 years, five meta-analyses, including more than 10,000 cases, showed that zinc supplementation significantly reduces the severity and duration of acute and persistent diarrhea in children aged < 5 years [28-30]. However, almost all the available evidence is based on children living in developing countries where zinc deficiency is a common condition.

A post hoc subgroup analysis by Patro et al. according to the nutritional status of enrolled children showed a greater effect of zinc supplementation in children severely malnourished than in those with none severe or no malnutrition [31]. Evidence is poor in nonmalnourished children. Whether zinc supplementation would be effective in countries where zinc deficiency is rare, such as European countries, is uncertain [28,31].

Additional studies are needed to establish the utility and efficacy of zinc supplementation in areas where zinc deficiency is not a problem.

Research is also needed to define fully the mechanism of action of zinc in the management of acute diarrhea in children [32].

4.2 Probiotics

Probiotics may be effective for acute diarrhea, in adjunct to ORS [33,34]. Compelling proof of efficacy is limited to few strains, specifically Lactobacillus rhamnosus GG (LGG) and the yeast Saccharomyces boulardii [35]. For many strains, data are preliminary and far from convincing. Also, while it is thought that probiotics modify the composition of the colonic microflora and act against enteric pathogens, their mechanism of action have yet to be defined [36]. Clinical data are fundamental to evaluate strain efficacy. The level of proof is 'conclusive' for LGG. A meta-analysis of trials focusing on this strain showed a significant reduction in the duration of diarrhea (weighted mean difference, WMD -1.1, 95% CI -1.9 to -0.3 days), especially in rotavirus-associated infection (WMD -2.1, 95% CI -3.6 to -0.6 days) [30]. The other effective probiotic organism is S. boulardii. A meta-analysis showed that S. boulardii was moderately effective in reducing the duration of diarrhea in otherwise healthy children with acute diarrhea (WMD -1.1, 95% CI -1.3 to -0.8 days), although the evidence-base was smaller than for LGG [37]. However, a comparative trial with five different probiotic preparations showed that only two were effective, indicating that many of the commercially available products do nothing for symptom duration and severity of gastroenteritis [36]. The increasing availability of new strains highlights the need for reassessment of effective preparations, with specific emphasis on stool output and other established parameters of efficacy. In addition, the clinical setting and the target of probiotics should be better defined. Finally, a specific issue is the optimal dose of probiotics and optimal time for administration. Although probiotics are living organisms, a dose-effect relationship is likely as with any biological phenomenon and should be investigated. At present a dose response effect is based on indirect evidence only [39]. In contrast to zinc, studies on the efficacy of probiotics have been done almost exclusively in developed areas, and the evidence of efficacy is limited to developing countries. In addition, recent guidelines produced in India do not recommend the use of probiotics because of the lack of evidence [40]. Malnutrition and the high incidence of bacterial agents may explain the limited efficacy of probiotics. However, more data are needed to assess the role of probiotics in developing countries, especially in preventing the progression from acute to persistent diarrhea and associated malnutrition.

4.3 Racecadotril (acetorphan)

Racecadotril (acetorphan) may be considered in the management of acute diarrhea in children [41], based on the evidence of significant reduction in the duration of diarrhea in hospitalized children in different areas (Peru [41] and France [42]). Stool volume was also reduced in one trial [27]. These data
Table 1. Overview of effective options for active treatment of diarrhea in adjunct to ORS, based on ESPGHAN/ESPID guidelines [1].

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of evidence of efficacy</th>
<th>Outstanding issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc supplementation*</td>
<td>Good; clinically relevant reduction in the duration and severity of diarrhea (in controlled trials in developing countries)</td>
<td>Uncertain efficacy in children without zinc deficiency</td>
</tr>
<tr>
<td>Probiotic strains*</td>
<td>Good but strain-specific GG and Saccharomyces boulardii; significant reduction of diarrhea duration (in meta-analyses and controlled trials); no clear effect on stool output</td>
<td>If given with ORS, the dose may be insufficient to obtain clinical effects</td>
</tr>
<tr>
<td>Racecadotril*</td>
<td>Good; significant reduction of stool output (in 1 clinical trial and diarrhea duration in 3 controlled trials)</td>
<td>Highly effective against viral diarrhea but not in bacterial diarrhea; mechanism of action requires further investigation; risk of antibiotic resistance</td>
</tr>
<tr>
<td>Smectite*</td>
<td>Good; significant reduction of stool output (in 2 trials) and diarrhea duration (in meta-analyses and controlled trials)</td>
<td>Effective on stool volume in inpatients, need for well-designed studies in outpatient populations to evaluate efficacy and safety; need for well-designed studies in the outpatient setting in developed countries; mechanism of action requires further investigation; safety issues</td>
</tr>
<tr>
<td>Loperamide1</td>
<td>Limited (lack of adequate trial data to support use; methodological issues in available trials)</td>
<td>Should not be used in infants and young children for potentially severe side effects</td>
</tr>
<tr>
<td>Kaolin-pectin1</td>
<td>Poor (lack of adequate trial data to support use)</td>
<td>No clinical trial data</td>
</tr>
<tr>
<td>Activated charcoal1</td>
<td>None</td>
<td>Possible effect on stool output (one study); limited data</td>
</tr>
<tr>
<td>Bismuth subsalicylate1</td>
<td>Poor</td>
<td>Tolerability issues; potential risk of Reye syndrome</td>
</tr>
<tr>
<td>Herbal medicine1 (e.g., Potentilla tormentilla1)</td>
<td>Poor (lack of standardization in the preparation)</td>
<td>Lack of clinical trial</td>
</tr>
<tr>
<td>Folic acid1</td>
<td>None</td>
<td>(supported by limited clinical data - only 1 trial)</td>
</tr>
<tr>
<td>Glutamine1</td>
<td>Poor</td>
<td>Lack of adequate trial data to support use in setting of acute diarrhea</td>
</tr>
<tr>
<td>Actapulgite1</td>
<td>Poor</td>
<td>Lack of adequate trial data to support use</td>
</tr>
<tr>
<td>Nitazoxamide1</td>
<td>Poor (lack of trial data to support use in the general population; independently of etiology)</td>
<td>Lack of adequate trial data to support use</td>
</tr>
<tr>
<td>Prebiotics1</td>
<td>None</td>
<td>Effect strongly dependent on pathogen</td>
</tr>
</tbody>
</table>

* Products that demonstrated strong efficacy in different setting.
1Products with poor or limited evidence of efficacy.
2See (63).

ESPGHAN/ESPID: European Society of Pediatric Gastroenterology, Hepatology and Nutrition and European Society of Pediatric Infectious Diseases;
GG: Lactobacillus rhamnosus GG strain; ORS: Oral rehydration solution.

were reviewed and it was concluded that racecadotril has some evidence of efficacy, but more data are needed [43]. Subsequently, it was reported that racecadotril had no effects on stool number and total duration of gastroenteritis in an outpatient setting [44]. In addition, also for racecadotril, the mechanism of antidiarrheal activity is not clear, although it may be related to a selective inhibitor of enkephalinase leading to a reduced transepithelial secretion [45]. There are methodological issues and limited data in outpatients that limit the interpretation of results on racecadotril efficacy. However a recent meta-analysis including more than 1300 in- and outpatients reported that racecadotril has a clinically relevant effect in reducing diarrhea (duration and stool output and number), and this effect was independent of baseline states (dehydration, rotavirus), treatment conditions (inpatient or outpatient studies) or between-country cultural disparities [46].

4.4 Diosmectite

Diosmectite is a naturally multilamellar aluminium-magnesium clay silicate, widely used to treat acute diarrhea in several countries. A meta-analysis combined data from six randomized controlled trials showed that diosmectite significantly reduced the duration of diarrhea (WMD -22.7 h, 95% CI -24.8 to -20.6 h) with a fixed model; the effect remained significant when data were analyzed with a random effects model [47]. Treatment was associated with increased likelihood of cure at day 3 (relative risk 1.64, 95% CI 1.36 - 1.98; number needed to treat to resolve one case of diarrhea = 4). In a large sample study in an outpatient setting in Italy, diosmectite reduced the duration of diarrhea and decreased the risk of its protracted (> 7 days) duration [48]. Despite the evidence of efficacy on duration of diarrhea, the doubtful effect of smectite on stool output has represented a matter of concern and some authors interpreted the effect of
smeets a 'cosmetic', indicating a more solid appearance of stools, without any changes in their volume [49]. However, two recent placebo-controlled trials, in Peru (n = 300) and Malaysia (n = 302), showed that treatment with diosmectite significantly reduced stool output over the first 72 h and this effect was maximal in children with rotavirus-positive infection [50]. This latter finding is clinically relevant given the burden of rotavirus infection in both developed and developing countries.

Therefore, evidence for efficacy of diosmectite is very broad including developed and developing countries and inpatient and outpatient settings. The mechanisms implicated in the anti-diarrheal effect include, increased colonic mucin secretion and modulation of cytokine production by mucosal cells [51], as well as effects on intestinal permeability [52] and blockade of water and electrolyte secretion [53]. A mechanism of action based on multiple effects is supported by the present understanding that rotavirus induces diarrhea through a sequence of functional and structural events on the enterocyte [54]. As a consequence, diosmectite could be highly beneficial against rotavirus, but also effective against a broad pattern of enteric pathogens that induce diarrhea through either enterotoxic or cytotoxic mechanisms.

4.5 Antibiotics

Antibiotic therapy is not needed in the vast majority of otherwise healthy children with acute gastroenteritis.

Despite the overall goal of improving clinical symptoms and preventing complication, antibiotics are not indicated in common cases of acute gastroenteritis because of:

- Poor evidence of efficacy of antibiotics even in bacterial gastroenteritis.
- Inconsistency between \textit{in vivo} and \textit{in vitro} susceptibility of causative agents.
- Worldwide increase of bacterial resistance (such as \textit{Shigella}) to antibiotics.
- Risk for inducing a state of healthy carrier in case of \textit{Salmonella} infection.

Antibiotic therapy could be indicated in defined clinical settings or selected cases in which a specific pathogen has been isolated. For example, several well-designed studies have shown that an appropriate antibiotic treatment of \textit{Shigella} (e.g., azithromycin or ceftiraxone) gastroenteritis may improve symptoms and reduce fecal excretion of the pathogens [5]. Eradication should be pursued in hospitalized, institutionalized children or those attending daycare. In similar settings also, an acute gastroenteritis caused by \textit{Campylobacter} could be considered an indication to treatment to be started within 3 days after disease onset [51]. Diarrhoegenic \textit{Escherichia coli (STEC), Vibrio cholerae} and \textit{Clostridium difficile} treatment may be considered for specific treatment based on the severity of symptoms.

5. Implementation of guidelines and actions for improving management of diarrhea

There are several guidelines on the management of acute gastroenteritis and their quality ranges from satisfactory to excellent. This has been recently shown in a work conducted using the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument, a standard validation tool to score guidelines quality [53]. The major problem with guidelines is their application in different settings. A number of outstanding issues may limit the applicability of trial data to current practice. These include the need for trials in inpatients and outpatients and in developed versus developing countries, the definition of patient group and also the importance of local factors including culture and beliefs. Implementation of clinical guidelines requires a multifaceted approach [56]. The application of guidelines to clinical practice can be measured as a gap between what is actually done and what should be done in an established clinical condition according to guidelines. The quality of care delivered to children in an ambulatory setting is far from good, ranging from 40 – 70% even in optimal conditions [57].

The key points in acute gastroenteritis include prevention, rehydration, microbiological investigations, nutrition and drugs. The management of acute gastroenteritis is based now on the option of 'doing the least': ORS administration, early refeeding, no testing, no unnecessary drugs [20,55]. However, recent guidelines support the concept of active treatment of gastroenteritis with drugs that have evidence-based efficacy.

Some authors are confident that the application of therapies and interventions that have already been demonstrated as effective could significantly reduce morbidity and mortality for diarrhea worldwide. Others, by contrast, feel that more direct evidence is needed in developing countries and point out the cost of treatments that could be only marginally effective in modifying the course of the disease.

Recently, Fischer-Walker and colleagues estimated, by using a modeling exercise, that the implementation of a multifaceted intervention based on both preventive activities (such as breastfeeding, vitamin A supplementation, hand washing, improved sanitation and drinking water sources, rotavirus vaccination) and treatments (including ORS, zinc and antibiotics for dysentery) could reduce diarrheal deaths by as much as 80% by the end of 2015 [58].

6. Costs and efficacy

With increasing requirements for financial restraint, cost-effectiveness analyses are a crucial part of any medical approach. The cost of an episode of diarrhea is not negligible. A previous paper by Avendano \textit{et al.} estimated the cost of an episode of acute diarrhea in an outpatient setting in the USA to be high at US$300 (US$325 for rotavirus-diarrhea, which
Table 2. Total costs and incidence of productivity loss for one episode of acute gastroenteritis induced by rotavirus in a child seen in primary care setting.

<table>
<thead>
<tr>
<th></th>
<th>Total costs (mean; €)</th>
<th>Loss of productivity (%)</th>
<th>No. of working days lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>473</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>France</td>
<td>321</td>
<td>56</td>
<td>2.5</td>
</tr>
<tr>
<td>Germany</td>
<td>432</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Italy</td>
<td>292</td>
<td>61</td>
<td>3.9</td>
</tr>
<tr>
<td>Spain</td>
<td>166</td>
<td>42</td>
<td>4.4</td>
</tr>
<tr>
<td>United</td>
<td>375</td>
<td>36</td>
<td>2.9</td>
</tr>
<tr>
<td>Kingdom</td>
<td></td>
<td>73</td>
<td>4.3</td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified by permission of Oxford Journals [63].

7. Conclusions

Acute diarrhea is still associated with substantial morbidity and mortality, especially in developing regions. Given the frequency of the problem, there are major cost implications, especially taking into account societal perspectives. The expert group highlights a number of actions that could improve the management of diarrhea [summarized in Box 2] to reduce substantially the burden of childhood acute diarrhea at a global level. These actions cover a broad spectrum, ranging from prevention to education, to research, to economic analysis. A multifaceted strategy is greatly needed.

8. Expert opinion

Acute gastroenteritis has been the target of a number of interventions on a global scale in the last 10 years, and the management of acute gastroenteritis has substantially improved. Oral rehydration solution was defined as the most important drug of the 20th century, based on the number of deaths spared with its use. The concentration of Na+ in the classic WHO/Unicef formulation has been reduced (as an option) to 75 mmol/liter of Na+, a concentration able to treat both cholera and noncholera diarrhea, and 60 mmol/liter is most probably effective in the vast majority of cases. However, in developed areas, where diarrhea-related death is not an issue, most children tend to refuse ORS with high Na+ concentration owing to the taste. Whether this would ultimately lead to a different ORS in developed and developing countries as it is progressively seen, or trigger a reevaluation of a putative universal ORS composition should be discussed. The trend is towards a reduction of Na+ content in parallel with a progressive decrease of the risk of cholera.

Also, the nutritional management during acute gastroenteritis has changed and the concept of refeeding is obsolete, being replaced with the concept of continuing nutrition with regular food including formula or milk in the vast majority of cases.

In parallel, new drugs have been made available and new proofs of efficacy have been provided for some of them. Active treatment of diarrhea is a priority on a global scale. Mothers ask for effective drugs independently of a mild (or less mild) course of the disease or their setting. In the past there was a general ‘opinion against’ the use of drugs for acute gastroenteritis. There was little proof of efficacy and, in addition, there was a fear that drugs would detract attention from the main intervention, that is oral rehydration. In parallel, a major field of intervention was manipulation of diet, with exclusion of lactose from milk, milk from the diet, of cow’s milk protein from infant nutrition, or even of any nutrition for a limited time during the acute phase of diarrhea. Today feeding is no longer a target of therapy, but there is an increasing trend towards the use of drugs.

Widespread use of effective drugs may deeply change the impact of acute diarrhea. Early use of ORS (which remains a priority), associated with effective drugs, may prevent...
hospitalization either by reducing the intensity of symptoms but also by providing a relief to anxious mothers. This may turn into an additional benefit in limiting hospitalizations.

Interestingly, out of the many drugs proposed for management, only a few show proof of efficacy, and for very few of them the efficacy is supported by solid evidence (i.e., meta-analysis). Epidemiology and etiology of acute gastroenteritis is only relatively affected by local conditions and the pattern is rather similar in different settings, with rotavirus consistently being the top agent. In contrast with such a universal pattern, the approach to gastroenteritis often reflects local trends (and marketing) conditions. A major effort is needed to exploit the concept of having a universal treatment, or a limited number of evidence-based therapies, in addition to ORS.

On the other side of the management of acute gastroenteritis is prevention. The availability of effective vaccines against rotavirus provides a major opportunity for not only reducing the global burden of the disease and substantially preventing its most dangerous consequences to children’s health, but also for limiting the fear of the disease. Again, the goal is to promote optimal management of the problem with interventions that are easy to apply and have no risk. Prevention is expensive, however, and rich countries should support it particularly in countries where acute diarrhea is still a major threat to the health of children. This should be done by contributing to the cost of the vaccine and its use. It is disappointing that, with the exception of the USA and a few countries in Europe, rotavirus vaccination is far from being implemented where there is effective infrastructure and enough financial support.

However, effective interventions, both in the field of management and of prevention, are still poorly applied and there is a major gap between what we could do and what we actually do. Maybe it is time for a ‘yes we can’ approach.

**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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**Bibliography**

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


This is an evidence-based guideline summarizing the available evidence for the management of children with acute gastroenteritis in Europe. It represents the most recent and updated document produced by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases on this issue.


8. A multicenter prospective trial carried out in 12 hospitals verified in four different European countries, studying the burden of rotavirus diarrhea in hospitalized children.


An authoritative document that summarizes the evidences of efficacy, recommendations and schedule for the rotavirus vaccination in European children.


12. A prospective surveillance conducted in two different areas in the USA, aimed at determining the burden of rotavirus in both hospital-based and outpatients settings before the vaccination distribution.


This is a recent study summarizing the data on rotavirus vaccination impact during the last 3 years in the USA.
Management of acute diarrhea in children

Authors reported that hospitalizations, emergency department visits and outpatient visits due to gastroenteritis have declined dramatically since the introduction of the vaccination policy.


- The official document of recommendation of the RotaTeq vaccine against rotavirus developed by the Advisory Committee on Immunization practice after the FDA approval obtained in February 2006.


- Recent and well-written evidence-based guidelines for Australian physicians discussing available evidence according to local policies and availability of drugs (such as probiotics not on the Australian market).


- Evidence-based guidelines for preschool children with acute diarrhea with or without vomiting, with the most updated recommendations for UK physicians and healthcare workers. Produced by the National Institute for Health and Clinical Excellence (NICE).


- An excellent and updated evidence-based document including recommendations for children aged 2 months to 18 years. These guidelines do not include some treatment (such as Smecta and Ruscudotril) unavailable in the US market.


- A well-conducted, randomized, controlled field trial demonstrating the effectiveness and clinical efficacy of an educational intervention in improving general pediatricians’ practice and clinical outcomes in children with acute diarrhea.


- A rigorous meta-analysis on the evidence on zinc supplementation for children with acute diarrhea. The authors reported the efficacy of zinc in children in developing countries but ask for additional evidence in developed areas.


- An extensive systematic review on the use of zinc in children, mainly based on data on children living in developing countries.


oxide-mediated ion secretion in human enterocytes. Eur J Pharmacol 2010;626:206-70


The most recent and outstanding meta-analysis summarizing the evidence available on the efficacy of probiotics in children and adults with acute diarrhea. Numerous subgroup analyses were performed, and the importance of concepts like dose, strain and age-dependent effects of probiotics are highlighted.


The most recent meta-analysis focused on the role of LGG in pediatric acute gastroenteritis.


The most recent meta-analysis focused on the role of Saccharomyces boulardii in pediatric acute gastroenteritis.


The only head-to-head study that compares the effect of different probiotic strains in children with acute diarrhea, underlining the strain-dependent efficacy.


First controlled trial studying the efficacy and safety of raccadotril in hospitalized children with acute diarrhea. Authors reported a significant beneficial effect in children administered raccadotril in terms of stool output, duration of diarrhea and need of oral rehydrating solution.


A recent trial on the efficacy of raccadotril, in outbreaks, which does not confirm the efficacy demonstrated in hospitalized children. Symptoms of diarrhea did not improve in children administered raccadotril compared with standard rehydration therapy.


The largest clinical trial on sucrose as an antidiarrheal drug in childhood.


Management of acute diarrhea in children


**This well-conducted study analyzes the quality of care in different areas of the USA, demonstrating, as already reported for adults, that adherence to standard of care is poor for different pediatric illnesses (including acute diarrhea).**


*An interesting exercise that estimates the potential impact of a multifaceted approach based on prevention and treatment interventions in different countries worldwide on the mortality for acute diarrhea in the next 5 years.*


**A prospective multicenter epidemiologic study focused on the economic burden of rotavirus gastroenteritis in Europe.**


**Affiliation**

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CHAPTER 3.
THE IDENTIFICATION OF RELEVANT CLINICAL OUTCOMES
IN INFECTIOUS DISEASES

3.1 The Consensus Group on Outcome Measures Made in Pediatric Enteral Nutrition: COMMENT Initiative

A standard definition of outcomes measures is a essential point in the evidence-based process to 1) accurately assess the efficacy of interventions; 2) compare results of different studies and/or different interventions; 3) monitor process in the time and assess the effect of changes in practice. The change in definition of outcomes and in the way of measuring it may significantly affect the evaluation of results.

In many fields of medicine a high heterogeneity in definitions has been reported; one example has been reported in a recent systematic review of 138 RCTs studying the effects of different interventions applied to children with acute diarrhea. In this review Johnston and colleagues found that 64 different definitions of diarrhea, 69 definitions of diarrhea resolution and 46 unique primary outcomes were used [1].

The key question is: How can we consider an intervention effective and appropriate if the definition of illness and healing, and the way choose to measure them are not reliable and standardized? Only the use of standardized definitions of illness, severity and healing or compliance and poor outcomes can lead to reliable and comparable results, and consequently allow an active monitoring of processes in the time.

In addition, in many cases researches focus on indices that may not be relevant to child health or quality of life.

Nutrition in infancy and childhood markedly influence relevant functional and health outcomes on a short- and long-term basis [2, 3]. During infancy, nutritional habits must meet the physiological nutrient requirements and support healthy growth and normal development.
Many different nutritional interventions have been proposed and tested to improve or optimize child development. Also the ESPGHAN provided guidance documents and promoted clinical trials to develop recommendations on the efficacy and benefits of many nutritional interventions and innovations; however conclusions still remain uncertain and controversial in many fields, for example the addition of compounds with proposed probiotic and prebiotic effects to infant foods that has been recently highlighted by the ESPGHAN Committee on Nutrition [4].

There is still no agreement within the scientific community about how to best define and measure outcomes used in nutrition trials conducted in infants and young children [5]. The use of inappropriate outcome measures and/or their definitions may result in misleading information on the relevance of the outcome measure for infant health. It also may result in overestimation, underestimation or failure to reveal potential benefits of the intervention [5].

Moved by these features, in 2012, a group constituted by members of the Committee of Nutrition of the ESPGHAN, the Early Nutrition Academy and the Child Health Foundation promoted an initiative named Consensus Group on Outcome Measures Made in Pediatric Enteral Nutrition Clinical Trials (COMMENT). The main objectives of this initiative are to:

1) To agree upon a range of outcome measures relevant to nutrition trials in children below 3 years of age;
2) To agree upon an updated ‘core data set’ that should generally be recorded in nutrition trials in infants and young children, and
3) To provide guidance on the use of surrogate markers in pediatric nutrition research.

With the final aim of driving the future research in the filed of pediatric nutrition and provide a standard core outcome set for the development of future clinical trails in that filed.

In details the participants discussed these objectives and agreed to set up six minor working groups whose coordinators and objectives are reported in Table 3.1.

**Table 3.1 COMMENT Working Groups with respective coordinators and field of work**

<table>
<thead>
<tr>
<th>Working Group - Topic</th>
<th>Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>Prof. Kim Fleischer Michaelsen</td>
</tr>
<tr>
<td>Acute diarrhea</td>
<td>Prof. Hania Szajewska</td>
</tr>
<tr>
<td>Atopic dermatitis and cows’ milk protein allergy</td>
<td>Prof. Christophe Dupont</td>
</tr>
<tr>
<td>Respiratory Infections</td>
<td>Prof. Alfredo Guarino</td>
</tr>
<tr>
<td>‘Gut comfort’ (e.g. colic, constipation, bloating)</td>
<td>Prof. Marc Benninga</td>
</tr>
</tbody>
</table>
The methodology used to define the most appropriate outcome measures in different fields of infant medicine was based on the following steps:

1. Isolation and comparison of the outcomes currently reported in literature for each topic. To reach the first goal a systematic search in MEDLINE, EMBASE and the Cochrane Library was performed by using appropriate search terms and filters according to each specific topic;

2. Determination of which outcomes to measure in clinical trials. Since the best strategy for selecting outcomes for clinical trials in children is currently not known [6], the working groups chose the Delphi technique. This is a structured method for reaching consensus in which opinions are sought from individuals and the collated results are fed back to the group as a whole to generate further discussion and finally reach an agreement [7, 8]. The Delphi method’s main advantage is anonymity, which allows for freedom of expression and also protects from any individual dominating a discussion, as can happen during a discussion or face-to-face debate [8];

3. Identification of outcomes of highest relevance in clinical trials from different perspectives (ie. clinicians/researchers, patients or their families, representatives from industry and regulatory people);

4. Definition of a core outcome set to be used for future trials in the field of interest.

### 3.2 Results of the COMMENT working group on respiratory infections

The Working Group on respiratory infections was coordinated by Prof. Alfredo Guarino and aimed at defining criteria for assessing key outcomes in pediatric nutrition trials in the field of respiratory infections.

We critically reviewed clinical trials studying the impact of nutritional interventions on upper (URTI) and lower (LRTI) respiratory tract infections. We focused on definitions, key outcomes, settings and confounding factors. A standardized table of evidence including author, year of publication and journal, type of trial, target population, intervention, control, primary outcomes and definitions of respiratory illness, clinical outcomes and the assessment of biomarkers to
measure the effects of nutritional interventions on respiratory outcomes was prepared. In papers including respiratory and non-respiratory clinical outcomes, only data related to respiratory clinical features and related definitions were reported in the table of evidence.

The electronic and bibliographic research identified 107 suitable references. After abstract screening and application of study inclusion criteria, 50 papers were included, 46 focusing on prevention of respiratory episodes and 4 on treatment.

Trials included in our analysis were published between 1991 and 2012 (21% between 1991 and 1999 and 79% between 2000 and 2012).

**Interventions**

The nutritional interventions applied in the analyzed studies were broad and included infant formulas and yogurt (enriched with various prebiotics or probiotics and/or micronutrients), vitamins and micronutrients supplementation and other interventions.

**Definitions**

A specific segmental definition of upper or lower respiratory tract infections was reported in 45/50 (90%) trials. In 5 trials, no definition of respiratory infections was reported. In 15 of the 50 analyzed trials, the definitions of URTI, LRTI and acute otitis media were based on a specific diagnosis made by a pediatrician (rhinitis, laryngitis, tracheitis, pharyngitis, sinusitis, otitis, common cold/influenza). In 30 trials, the definition of URTI or LRTI was based on clinical symptoms reported by families or field workers (runny nose, cough, sore throat). Lower respiratory tract infections included pneumonia, bronchitis, wheezing and bronchiolitis. The specific diagnosis was usually made based on cough, abnormal respiratory rate according to age, crepitation to chest auscultation and chest indrawing, and was supported by radiographic findings in some cases.

In some trials, other systemic symptoms and signs such as fever, headache, restlessness, shortness of breath and acute ear pain, were added to the respiratory features to further support diagnosis.

Fever was reported in 22 out of 50 trials reported as a feature associated to URTI or LRTI although a specific definition of fever was provided only in 8 papers (36%) and the cut-off temperature values varied, with a rectal temperature >38°C being the most common definition. The temperatures were usually reported by parents or field workers, and the duration of each episode was recorded in days (rather than hours).
The most relevant result is the huge heterogeneity in definitions used in trials. Overall we found 13 different definitions of LRTI, 5 of URTI and 3 of fever.

Outcomes
Incidence, prevalence and duration of specific respiratory symptoms (eg. cough with or without fever) were the main outcomes in prevention trials. Duration of symptoms or hospitalization, and symptom-free periods were the main outcomes in the only 4 trials on treatment. Some trials included quantitation of antibiotic prescriptions, absence from daycare or school, or medical visits as surrogate end-points, even if in no case a specific definition was provided. In addition, in many trials the “definition” of diseases, as well as the diagnosis of respiratory infection, was committed to field workers of even to family members; this evaluation might significantly affect the reliability of the results.

Conclusion and further research steps
Considering the current scenario and the relevant heterogeneity reported, a straightforward definition of outcome measures seems to be needed to ensure a more reliable and consistent reporting of data.

We hypothesized to differentiate outcomes into two categories: “direct” and “indirect” outcomes. The “direct outcomes” would be aimed at assessing the efficacy of a selected intervention on respiratory diseases. These outcomes, including the incidence or the severity of selected infections (otitis, URTI, pneumonia), should be measured by well-trained personnel (eg. physicians) who make a specific diagnosis. In that case definitions should be based on updated guidelines. On the other side, the “indirect outcomes”, such as the number of performed chest-X-ray, working-day loss, medical visits and interventions or hospitalization, may provide a reliable estimate of the burden of respiratory diseases on health-care. These simple, easy-to-measure end-points may be monitored by field workers or, even, family members (if trained), bypassing the need to use difficult or complex diagnostic criteria, or validated scores.

The article by Guarino et al. [9] here attached reports in details the finding of this first phase of the Working Group. However, based on the above reported approach the Working Group developed a questionnaire reporting the main outcome measures distinguished in direct and indirect outcomes. To complete the phase 4, the questionnaire has been circulated among 1) the authors of previously published trials on the use of nutritional intervention aimed at prevent or treat
respiratory infections, 2) expert of the ESPGHAN Society, 3) experts of the ESPID Society and 4) participants to international congress on gastroenterology and infectious diseases with the aim of grading the 3 most relevant outcomes for each category (direct and indirect outcomes).

3.3 Results of the COMMENT working group on acute diarrhea

The Working Group on acute diarrhea was coordinated by Prof. Hania Szajewska. For the first phase of the project the group referred to the review performed by Johnston and colleagues [1], and begins from that point to identify the definitions of diarrhea, resolutions, scores and markers. Once identified the outcomes reported in literature, the group developed an electronic questionnaire with two open-ended questions to identify potential outcomes and distributed it to clinicians/researchers, industry representatives and members of regulatory bodies. Members of ESPGHAN and ESPID were invited to participate in the electronic Delphi survey, along with representatives from industry, regulatory people and researchers. The responders were asked to consider which outcomes should be measured in clinical trials related to acute diarrhea in both inpatient and outpatient settings. A similar, simplified questionnaire was developed for parents. Parents of children admitted to the hospital due to acute diarrhea in Belgium, Italy, Israel and Poland were invited to participate in the first round of the Delphi survey of parents. A second phase included the definition of a short list of clinically relevant outcomes selected from those listed by at least 10% of participants in phase 1. This list was proposed to the evaluation and responders were asked to consider which outcomes should be measured in clinical trials related to acute diarrhea in both inpatient and outpatient settings. Two types of question were created for this part—one ranking each outcome on a scale of 0 (unimportant) to 4 (very important) and the other asking responders to select the five most important outcomes in their opinion [8].

Clinical questionnaire

A total of 64 responders, including ESPGHAN members, ESPID members, researchers, regulatory body members and industry representatives, completed the 2 phases. In the outpatient setting, the need for hospitalization, diarrhea duration and dehydration were
clearly considered to be the most important outcomes of treatment. In the inpatient setting, on the other hand, hospital stay, diarrhea duration, dehydration and the use of intravenous rehydration therapy were seen as the most relevant outcomes to be included considered.

Parents’ questionnaire
Thirty-two parents from Italy, Belgium, Israel and Poland took part to the phase 2. It was found that the most comforting aspects of treatment included the child behaving normally, seeming healthy and being willing to eat and drink, improvement of diarrhea and the medical visit, consultation and reassurance. The most worrisome aspects of treatment included bloody diarrhea, fever and the child’s worsening condition.

Conclusions and further research steps
So far, the Working Group on acute diarrhea has completed three out of four steps of the project. Once again a huge heterogeneity in reporting clinical outcomes was emerged in this filed as well as for respiratory infections. To date the identification of outcomes related to acute diarrhea are reported and the decision about the methodology for determining which outcomes to measure in clinical trials has been taken. The latter steps have been reported in the paper by Karas et al [8]. To complete the project, the working group needs to determine the outcome core set. It would additionally be very useful to ascertain the impact of this core outcome set creation and monitor its implementation in future trials.
3.4 References


3.5 Publications

   Definitions and Outcomes of Nutritional Interventions in Children with Respiratory Infections:
   The Approach of the COMMENT Initiative.

   of the Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical
   Trials (COMMENT).
   A core outcome set for clinical trials in acute diarrhoea.
   *Arch Dis Child* 2014;100(4):359-63.
Definitions and Outcomes of Nutritional Interventions in Children with Respiratory Infections: The Approach of the COMMENT Initiative

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**Key Words**
Nutrition • Children • Respiratory infections • Outcomes

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**Abstract**

**Background/Alms:** This study is aimed at assessing definitions and outcomes used to measure the effects of nutrition in the prevention and treatment of respiratory tract infections in childhood. **Methods:** We reviewed clinical trials studying the impact of nutritional interventions on upper and lower respiratory tract infections (URTI and LRTI), focusing on definitions and key outcomes. **Results:** Fifty trials were included (46 on prevention and 4 on treatment). The definitions of respiratory infections were highly heterogeneous. In 15 of the trials, URTI or LRTI were diagnosed by a pediatrician. In 30 trials, definitions were based on symptoms reported by family members or field-workers only. Five trials did not provide any specific definition. Incidence was the most common outcome measure reported in the trials on prevention, and duration and illness severity were the most common in the treatment trials. **Conclusions:** The results showed a major heterogeneity with the use of a wide array of different definitions and clinical end points. To overcome these limitations, outcome measures might be differentiated into two categories: ‘direct outcomes’ in which respiratory infections are diagnosed and monitored by physicians according to rigorous definitions and ‘indirect outcomes’ (e.g. chest X-ray, antibiotic prescription and hospitalizations) to assess the burden of respiratory illnesses. Agreement on standard definitions and end points is needed to drive future trials.

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**Introduction**

Acute respiratory infections (ARI), including both upper and lower respiratory infections (URTI and LRTI), are the most common illnesses worldwide during infancy [1]. The high rates of respiratory infections are associated with high social and family costs [2]. ARI are a major cause of missed work-days by parents and are responsible for a massive use of drugs and investigations.

Risk factors for ARI, in addition to host-related conditions, include environmental conditions such as seasonality (i.e. wintertime with higher rates of influenza, respiratory syncytial virus and other viruses) and selected settings such as daycare centers, schools and hospitals. Children attending daycare centers are at a 2- to 3-times greater risk...
for developing ARI than children at home [3]. Host-related conditions such as immune-compromising conditions, underlying chronic diseases and atopy are associated with an increased incidence and severity of ARI [4].

Scattered data suggest that selected nutritional interventions may reduce the risk of developing ARI. Probiotics, prebiotics, vitamins and micronutrients such as zinc have been used to reduce the incidence of gastrointestinal and respiratory infections in pediatric populations. Results are sometimes conflicting and often difficult to generalize. This may depend on factors such as population features (e.g. age, location, health status, risk factors and other therapies) and type of intervention (e.g. type of supplementation, formulation, dosage and duration of consumption), but may be even more strongly related to the difference in definitions and outcome measures that have been used.

The recently formed Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT) appointed specific working groups to identify and define criteria for assessing key outcomes in these trials. The overall aims of the COMMENT initiative are reported in detail in a previous paper by Koletzko et al. [5].

Inspired by the COMMENT initiative, a panel of experts including members of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Diseases (ESPID) decided to conduct a systematic review of the available data, to define the most appropriate criteria to apply in trials that study the effects of nutritional interventions for the prevention or treatment of ARI in children [5].

This study is aimed at reviewing the data from the trials, looking at the effects of selected nutritional interventions on ARI in infancy and early childhood, with specific attention paid to the definitions, clinical end points and markers used.

**Methods**

**Search Strategy**

We searched for clinical trials studying the effects of different nutritional interventions on ARI in children and infants. A research on MEDLINE (up to August 2012) and on the Cochrane Central Register of Controlled Trials (CENTRAL 2012) databases was performed, with no limit on article type or time, in order to obtain a full body of evidence to be selected afterwards.

Search terms included extensive controlled vocabulary and keyword searches for 'respiratory tract infections' [Medical Subject Headings (MeSH) and text words (tw)], 'influenza' (tw), 'otitis' (MeSH and tw), 'pneumonia' (MeSH and tw), 'infants' (MeSH and tw), 'child' (MeSH and tw), 'nutrition', 'infant formula' (MeSH), 'yoghurt' (MeSH and tw), 'prebiotics' (MeSH), 'probiotics' (MeSH), 'micronutrients' (MeSH), 'calcium' (MeSH and tw), 'vitamin' (tw), 'lipid' (MeSH), 'fat' and 'fats', 'carbohydrates' (MeSH) and 'protein' (MeSH).

To identify additional articles, references cited in the included trials were checked.

**Study Selection and Data Extraction**

We decided to include studies conducted on children up to the age of 6 years (preschool age), published in English, that include URTI or LRTI as primary or secondary outcomes, or biomarkers related to respiratory tract inflammation or infection episodes. Although the COMMENT project included infants and young children aged <3 years [5], we decided to extend the age range up to 6 years with the ultimate aim of including preschool children who more frequently develop respiratory infections and are the usual target population for such trials on respiratory infections. Any type of nutritional intervention was considered. However, administration of 'functional foods' as such, including prebiotics, probiotics or symbiotics not included in formulas or other foods, was not included.

Trials on populations with a wide age range including both target population (infant and preschool children) and older children were included, even if age-specific subanalysis was not reported. Trials that included only children ≥6 years of age were excluded.

Articles were selected based on the title and abstract, and the full text of all selected articles was retrieved and independently assessed for inclusion according to prespecified criteria by two independent reviewers (E.B. and A.L.V.).

A standardized table of evidence was prepared including author, year of publication and journal, type of trial, target population, interventions, controls, primary outcomes and definitions of respiratory illness, clinical outcomes and the assessment of biomarkers to measure the effects of nutritional interventions on respiratory outcomes. In articles including respiratory and non-respiratory clinical outcomes, only data related to respiratory clinical features and related definitions were reported in the table of evidence.

Descriptive statistics were used to describe the characteristics of trials and compare definitions used by researchers, interventions and outcomes.

**Results**

The electronic and bibliographic research identified 107 suitable references. After abstract screening and application of study inclusion criteria, 50 papers were included, 46 focusing on the prevention of respiratory episodes and 4 on treatment [6–55]. Figure 1 shows the flow-search diagram.

Trials included in our analysis were published between 1991 and 2012 (21% between 1991 and 1999 and 79% between 2000 and 2012). More than 90% were specifically conducted to evaluate the effects of nutritional interven-
tions in the prevention or treatment of respiratory tract infections in children, with 10% including respiratory end points as secondary outcomes.

**Study Populations**

The age of enrolled children ranged from 15 days to 15 years.

Fifteen studies (30%) included only infants, 28 (56%) included children up to 5 years. Others included children with wider age ranges including infants and older children (5 with an age range of 1 month to 15 years) or ages were not specified [2].

The majority (approx. 70%) of trials were conducted on healthy subjects. However, several studies evaluated the efficacy of specific nutrients in children with clinical conditions such as malnutrition. HIV infection or atopy as well as children who had been hospitalized, which potentially increases susceptibility to infectious diseases. Other important factors which could modify the risk of infectious disease were the socioeconomic status and the social setting. Both may influence nutrient availability, health assistance, prevention measures and case exposure. There was a community setting in 68% (34/50) of the trials; the rest investigated the effects of nutritional intervention in high-risk settings such as hospitals, daycare centers and schools. We included trials conducted in different locations, i.e. Africa: 9 (18%), North America: 5 (8%), South America: 7 (14%), Asia: 15 (31%) and Europe: 14 (29%). The sample size was very broad, ranging from 40 to 15,419 and the duration of the intervention ranged from days to several months (≤6 months in 68% of the trials).

**Interventions**

The nutritional interventions applied in the analyzed studies were broad and included infant formulas and yoghurt (enriched with various probiotics or probiotics and/or micronutrients) and supplementation with vitamins and micronutrients (table 1).
Table 1. Nutritional interventions administered in included trials

<table>
<thead>
<tr>
<th>Nutritional intervention, type</th>
<th>Duration of intervention</th>
<th>Trials, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemented and modified infant formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With probiotics</td>
<td>3 – 12 months</td>
<td>7</td>
</tr>
<tr>
<td>With prebiotics</td>
<td>1 – 12 months</td>
<td>2</td>
</tr>
<tr>
<td>With both prebiotics and probiotics</td>
<td>3 – 12 months</td>
<td>3</td>
</tr>
<tr>
<td>Lipids (DHA)</td>
<td>12 months</td>
<td>1</td>
</tr>
<tr>
<td>Fermented probiotic dairy drink</td>
<td>3 months</td>
<td>1</td>
</tr>
<tr>
<td>Fermented milk product with probiotics</td>
<td>a few days to 12 months</td>
<td>3</td>
</tr>
<tr>
<td>Supplementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronutrients, e.g. Ca, Zn and Fe</td>
<td>a few days to 12 months</td>
<td>11</td>
</tr>
<tr>
<td>Vitamins + micronutrients</td>
<td>a few days to 12 months</td>
<td>6</td>
</tr>
<tr>
<td>Vitamins</td>
<td>15 days to 24 months</td>
<td>12</td>
</tr>
<tr>
<td>Lipids, e.g. PUFA, cod liver oil and sesame oil</td>
<td>3 days to 6 months</td>
<td>2</td>
</tr>
<tr>
<td>Other nutrients</td>
<td>4 – 6 months</td>
<td>2</td>
</tr>
</tbody>
</table>

Definitions of URTI, LRTI and Acute Otitis Media

The definitions of respiratory infections were highly heterogeneous.

A specific segmental definition of URTI or LRTI was reported in 45/50 (90%) trials. In 5, no definition of respiratory infections was reported. In 15 of the 50 analyzed trials, the definitions of URTI, LRTI and acute otitis media (AOM) were based on a specific diagnosis made by a pediatrician (rhinitis, laryngitis, tracheitis, pharyngitis, sinusitis, otitis or common cold/influenza). In 30 trials, the definition of URTI or LRTI was based on clinical symptoms reported by families or field-workers (runny nose, cough or sore throat). LRTI included pneumonia, bronchitis, wheezing and bronchiolitis. A specific diagnosis based on cough, abnormal respiratory rate according to age, crepitations to chest auscultation and drawing in of the chest was made in most cases, and this was supported by radiographic findings in some.

In some trials, other systemic symptoms and signs such as fever, headache, restlessness, aphony, shortness of breath and acute ear pain were added to the respiratory features to further support the diagnosis. Fever was reported in 22 out of 50 trials reported as a feature associated with URTI or LRTI, although a specific definition of fever was provided in 8 papers (36%) only, and the cut-off temperature values varied with a rectal temperature of >38°C being the most common definition. The temperatures were usually reported by parents or field-workers, and the duration of each episode was recorded in days (rather than in hours).

The most common, specific definitions are reported in table 2.

The duration of episodes was considered as a major outcome of respiratory infection episode in 8 of the trials (3 were on treatment and 5 were on prevention). In 4 trials (50%), an episode started 24 h after the onset of symptoms, i.e. very brief or transitory episodes were excluded and in the other papers, at least 2 consecutive days of symptoms were needed to define a single episode. Recurrence was another important outcome in 19 trials, and a new episode was defined as coming after a symptom-free interval of 2, 7 or 14 days in 1, 2 or 4 trials, respectively.

Outcome Measures and Markers

Incidence, prevalence and duration of specific respiratory symptoms (e.g. cough with or without fever) were the main outcomes in trials on prevention. Duration of symptoms or hospitalization and symptom-free periods were the main outcomes in the 4 trials on treatment (table 3).

Some trials included quantitations of antibiotic prescriptions, absence from daycare or school, or even medical visits as surrogate end points, if no specific definition was provided (table 4).

Nonspecific markers related to respiratory tract infections or inflammation were also a topic in some of the studies. Some reported nonspecific laboratory markers of inflammation (e.g. C-reactive protein, white blood cell count, immunoglobulins, interleukins and retinol-binding protein) as secondary outcomes.
Table 2. Main definition of respiratory infections and fever considered in the included trials

<table>
<thead>
<tr>
<th>Outcome definitions</th>
<th>Trials, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower respiratory tract infections</strong></td>
<td></td>
</tr>
<tr>
<td>LRTI defined as cough or fever + cough or cough + rapid respiratory rate</td>
<td>7</td>
</tr>
<tr>
<td>LRTI as defined by physician (pneumonia, bronchiolitis, bronchitis or wheezing)</td>
<td>6</td>
</tr>
<tr>
<td>LRTI not specifically defined</td>
<td>6</td>
</tr>
<tr>
<td>LRTI defined as cough and respiratory rate &gt;40/min for &gt;2 consecutive days</td>
<td>5</td>
</tr>
<tr>
<td>LRTI defined by the presence of fever + cough + difficult breathing (for at least 1 day)</td>
<td>3</td>
</tr>
<tr>
<td>LRTI defined as cough for &gt;2 days with or without fever and wheezing and/or crepitations</td>
<td>2</td>
</tr>
<tr>
<td>LRTI defined as respiratory rate &gt;50/min</td>
<td>1</td>
</tr>
<tr>
<td>LRTI as defined by caregiver/field-worker</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia defined as respiratory rate &gt;40/min + drawing in of lower chest or fever (TC &gt;37.7°C)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia as an association of clinical symptoms and a positive culture</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia defined as cough and crepitations</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia defined according to history, clinical examination and chest X-ray</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia defined as crepitations and respiratory rate &gt;50/min or wheezing or bronchitis and crepitations</td>
<td>1</td>
</tr>
<tr>
<td><strong>Upper respiratory infections</strong></td>
<td></td>
</tr>
<tr>
<td>URTI as defined by physician (rhinitis, tracheitis, pharyngitis, sinusitis, otitis and common cold)</td>
<td>9</td>
</tr>
<tr>
<td>URTI defined as cough lasting &gt;2 days with or without fever, including rhinitis, pharyngitis, common cold, etc.</td>
<td>4</td>
</tr>
<tr>
<td>Influenza-like symptoms defined as fever, rhinorrhea and cough</td>
<td>1</td>
</tr>
<tr>
<td>Rhinitis defined as rhinorrhea, nasal obstruction, nasal itching and sneezing</td>
<td>1</td>
</tr>
<tr>
<td>URTI defined as colored nasal discharge, nasal congestion or cough or sneezing and nasal discharge</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
</tr>
<tr>
<td>Rectal temperature &gt;38°C</td>
<td>3</td>
</tr>
<tr>
<td>Axillary temperature &gt;37°C</td>
<td>2</td>
</tr>
<tr>
<td>Axillary temperature &gt;37.7°C</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

This study aimed to systematically review the definitions and outcome measures used in trials assessing the efficacy of nutrition in the prevention and treatment of respiratory tract infections in infancy and early childhood. The results showed a major heterogeneity, with the use of a wide array of definitions and clinical end points.

Such variability in defining disease episodes and end points could be partially related to the important role played by family members and/or field-workers in reporting conditions, particularly in the large field-trials on prevention. In this specific setting, definitions need to be broad and easy to measure, with the risk of losing some sensitivity but mainly specificity.

Different definitions of URTI and LRTI were used based on the presence and association of specific symptoms; however, the duration of these was rarely reported. Diagnosis of URTI was often based on a single symptom or on the presence of a cohort of different respiratory symptoms (runny nose, nasal congestion, laryngitis, pharyngitis or tracheitis). The association and the duration of the symptoms varied between studies. In most cases, the presence of symptoms was recorded by a member of the family of the sick child (usually the mother), but in some, the definition was based on the diagnosis made...

Table 3. Primary outcomes considered in interventional trials on nutrition

<table>
<thead>
<tr>
<th>Primary outcomes1</th>
<th>Trials, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention studies</td>
<td>46</td>
</tr>
<tr>
<td>Incidence of respiratory infections (URTI, LRTI and AOM)</td>
<td>34</td>
</tr>
<tr>
<td>Prevalence of respiratory symptoms (morbidity)</td>
<td>14</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>6</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>1</td>
</tr>
<tr>
<td>Treatment studies</td>
<td>4</td>
</tr>
<tr>
<td>Duration of respiratory episodes (in days)</td>
<td>2</td>
</tr>
<tr>
<td>Duration of hospitalization (in days)</td>
<td>2</td>
</tr>
<tr>
<td>Severity of respiratory symptom (cough)</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Some studies included more than one primary outcome.
by the physician and a specific (segmental) definition of URTI, rather than specific symptoms, was reported.

Criteria for the diagnosis of AOM were also poorly reported and heterogeneous throughout the studies. Tympanic membrane bulging is a key sign to differentiate AOM from otitis media with effusion [56], and the assessment of membranes through a pneumatic otoscopy is a prerequisite for the diagnosis. However, this requires a medical staff well-trained in pneumatic otoscopy [57], and may represent a barrier to including otitis among the outcome measures for large-scale studies.

In the case of LRTI, the definition was somewhat more consistent in the few articles that included it, also because the diagnosis was based on physician consultation and specific symptoms of LRTI (such as the increase of respiratory rate, crepitations to chest auscultation or drawing in of the chest) or else on radiographic findings.

Fever was frequently taken as an outcome measure, being easy to measure and monitor as well as providing information on the duration and, to some extent, on the severity of the disease. However, the reliability of body temperature measurements may vary widely according to instrument, environment and site of measurement. In addition, the definitions of fever were scattered with cut-off values ranging from 37 to 38.5°C.

Overall, most studies focused on prevention, the heterogeneity for primary outcomes was limited and the incidence of new URTI or LRTI episodes was the outcome measure most frequently used, despite the definitions not always being sufficiently detailed. In the majority of trials, important information such as time limits of intervention and observation was not included. Other potentially relevant details were often missing. Reference to the season, which can be a key risk factor for developing respiratory infections and usually included in the definition of community-acquired respiratory infections (e.g. winter season to define influenza or other respiratory viruses) was rarely found. Moreover, the wide age ranges of the study populations and the different study settings created major potential biases which affected the accurate assessment of respiratory infection outcomes. Some relevant markers specifically related to clinical outcomes, e.g. vaccination status with regard to influenza or Streptococcus pneumoniae, were not provided in the majority of cases that had been conducted after licensure of these vaccines.

Considering the current scenario and the relevant heterogeneity reported, a straightforward definition of outcome measures seems to be needed in order to ensure a more reliable and consistent reporting of data.

We hypothesized differentiating outcomes into 'direct' and 'indirect' outcomes. The 'direct outcomes' would be aimed at assessing the efficacy of a selected intervention on respiratory diseases. These outcomes, including the incidence or the severity of selected infections (e.g. otitis, URTI and pneumonia), should be measured by well-trained personnel (physicians) who make a specific diagnosis.

On the other hand, the 'indirect outcomes', e.g., the number of chest X-rays performed, medical visits and interventions or hospitalizations as well as the loss of workdays, may provide a reliable estimate of the burden of respiratory diseases on healthcare. These simple, easy-to-measure end points may be monitored by field-workers or even family members (if trained), thereby bypassing the need for difficult or complex diagnostic criteria or validated scores.

In conclusion, heterogeneity was revealed in the current literature on respiratory infections and problems arose when we compared the results of studies using heterogeneous definitions and end points. These factors highlight the need for 'guidelines' that agree on standard definitions and outcome measures in order to facilitate trials in the future that will be effective in assessing respiratory outcomes in childhood.

References


Respiratory Infections: Impact of Nutritional Intervention


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A core outcome set for clinical trials in acute diarrhoea

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ABSTRACT

Objective Core outcome sets are the baseline for what should be measured in clinical research and, thus, should serve as a guide for what should be collected and reported. The Consensus Group on Outcome Measures Made in Pediatric Enteral Nutrition Clinical Trials, established in 2012, agreed that consensus on a core set of outcomes with agreed-upon definitions that should be measured and reported in clinical trials was needed. To achieve this goal, six working groups (WGs) were setup, including WG on acute diarrhoea, whose main goal was to develop a core outcome set for trials in acute diarrhoea.

Methods The first step identified how published outcomes related to acute diarrhoea were reported. The second focused on the methodology for determining which outcomes to measure in clinical trials. The third employed a two-phase questionnaire study using the Delphi technique to define clinically important outcomes to clinicians and parents.

Results For therapeutic studies, the five most important outcome measures were diarrhoea duration, degree of dehydration, need for hospitalisation (or duration of hospitalisation in inpatients), the proportion of patients recovered by 48 h and adverse effects. The prophylactic core outcome set included prevention of diarrhoea, prevention of dehydration, prevention of hospitalisation and adverse effects.

Conclusions The outcome set for therapy and prevention can be recommended for use in future trials of patients with gastroenteritis. Their envisioned goal is to decrease study heterogeneity and to ease the comparability of studies. WG’s next step is to determine how to measure the outcomes included in the core set.

BACKGROUND

Differences in outcomes and how outcomes are defined and measured make it difficult, sometimes impossible, to synthesise the results of nutritional trials and apply them in a meaningful way. Non-uniform outcome selection and reporting leads to a difficulty in synthesising results and potentially to outcome reporting bias. Additionally, important outcomes may not be included, resulting in lower validity of the results. Recognising the problem, the Consensus Group on Outcome Measures Made in Pediatric Enteral Nutrition Clinical Trials (COMMENT) was established in 2012.1 COMMENT agreed that consensus on a core set of outcomes, with agreed-upon definitions on what should be measured and reported in nutritional trials, was needed. To achieve this goal, six working groups (WGs) were setup, including WG on acute diarrhoea. The main goal of this WG is to develop a core outcome set for clinical trials in acute diarrhoea.

METHODS

In order to achieve the main goal, four steps have been planned. The first step involved identifying how outcomes related to acute diarrhoea are reported. By searching MEDLINE, EMBASE and the Cochrane Library (search date: February 2009), we found one systematic review7 that identified 138 randomised controlled trials (RCTs) reporting on ≥1 primary outcomes related to paediatric acute diarrhoea/diseases. The included trials used 64 unique definitions of diarrhoea, 69 unique definitions of diarrhoea resolution and 46 unique primary outcomes. Overall, this systematic review documented substantial heterogeneity in acute diarrhoea...
diarrhoea outcomes. Furthermore, even in what would be considered methodologically sound clinical trials, definitions of diarrhoea, primary outcomes and measurement instruments employed in RCTs of paediatric acute diarrhoea lacked evidence of validity and focused on indices that may not be important to participants.

The second step of the project focused on the methodology for determining which outcomes to measure in clinical trials. A review of studies that address the process of selecting outcomes to measure in clinical trials revealed that the best strategy for selecting outcomes for clinical trials in children is currently not known. When deciding on our own methods, WG had the choice of the Delphi technique, the nominal group technique, a semi-structured discussion or a questionnaire-based survey. The Delphi technique was eventually chosen for its merits in comparison to the other options. This is a structured method for reaching consensus in which opinions are sought from individuals and the collated results are fed back to the group as a whole to generate further discussion and finally reach an agreement. The Delphi method’s main advantage is anonymity, which allows for freedom of expression and also protects from any individual dominating a discussion, as can happen during a discussion or face-to-face debate.

The aim of the third step of the project, which we are reporting here, was to identify outcomes of highest relevance in clinical trials on acute diarrhoea from different perspectives (i.e., clinicians/researchers, patients or their families, representatives from industry and regulatory people). Previously, Sinha et al. developed a pilot method for identifying outcomes of particular relevance when evaluating the effects of regular therapies for chronic childhood asthma from the perspectives of clinicians involved in the outpatient management of children with asthma, parents of children younger than 18 years and young people aged between 13 and 18 years. For this, paediatricians and specialist nurses, identified through the British Paediatric Respiratory Society, completed a two-round Delphi survey. It was recommended that others adopt this approach.

In May 2013, during the London meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), WG decided to adopt the methodology of the pilot study developed by Sinha et al. Thus, we performed a two-step questionnaire study using the Delphi technique. The process first involved identifying a long list of potential outcomes (Phase 1) and then defining a short list of clinically important outcomes (Phase 2). The study flowchart is given in Figure 1. The ‘facilitator’, as he is known in a Delphi survey, a member of WG, was responsible for collecting and analysing the results of phase 1.

Prior to the questionnaires being sent out, a predefined domain/subdomain and outcome classification was created by WG. It was based on the most common pre-existing outcomes and results from Johnston et al. and was analysed and selected by one of the WG members. It was then discussed and accepted by WG. It was decided that after the questionnaires were filled out and analysed, the results could be classified into the categories or, if needed, new categories could be created. The ‘facilitator’ was responsible for this as well, and acceptance and agreement was sought from WG. The predefined categories are summarised in online supplementary Table A.

**Phase 1**

**Clinical questionnaire**

In phase 1, an electronic questionnaire with two open-ended questions to identify potential outcomes was created for clinicians/researchers, industry representatives and members of regulatory bodies (see online supplementary figure A). Members of ESPGHAN and the European Society of Paediatric Infectious Diseases (ESPID) were invited to participate in the electronic Delphi survey, along with representatives from industry, regulatory people and researchers. The responders were asked to consider which outcomes should be measured in clinical trials related to acute diarrhoea in both inpatient and outpatient settings.

**Parents’ questionnaire**

A questionnaire for parents was also created (see online supplementary figure B). Parents from Belgium, Italy, Israel and Poland were invited to participate in the first round of the Delphi survey of parents. The parents selected for the study were those of children admitted to the hospital due to acute diarrhoea. The purpose of the study was explained to them, and they were asked to answer based on their own personal view.

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**Figure 1** Study flowchart. ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; ESPID, European Society of Paediatric Infectious Diseases.

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83
questions were asked in order to identify a long list of outcomes that could be relevant.

**Phase 2 Clinical questionnaire**

This step included defining a short list of clinically important outcomes. Thus, the outcomes listed by at least 10% of participants in phase 1 were forwarded to phase 2. Questions in the phase 2 clinical questionnaire were based on the updated domain/subdomain and outcome classification (see online supplementary table A). In comparison with the predefined classification, subdomains such as the need for antibiotics, the need for other medication (eg, antimotility agents) and the use of intravenous rehydration therapy were added. Additionally, some minor phrasing changes were made and ‘weight change’ was divided into ‘weight loss’ and ‘weight gain’. Importantly, although ‘probiotics’, ‘functional status’ and ‘parental cooperation’ were mentioned by >10% of responders, WG decided not to include them as they are not actually ‘outcomes’ and thus do not merit inclusion. The reason for not including ‘functional status’ was the ambiguity of this term, which could confuse clinicians among responders. The responders were asked to consider which outcomes should be measured in clinical trials related to acute diarrhoea in both inpatient and outpatient settings. Two types of question were created for this part—one ranking each outcome on a scale of 0 (unimportant) to 4 (very important) and the other asking responders to select the five most important outcomes in their opinion (see online supplementary figure C). The same group of individuals who had participated in phase 1 and had also agreed to take part in phase 2 was invited. At no point did the individuals know the results of phase 1.

**Parents’ questionnaire**

Outcomes listed by at least 10% of participants were carried forward to phase 2. In phase 2, just as for clinicians, closed-ended questions would be employed to identify the most important outcomes (see online supplementary table B). As a result, a more targeted email was sent out to around 100 people, who included ESPGHAN and ESPID members, researchers, members of regulatory bodies and industry representatives. In the end 70 responses were received, with 64 responders agreeing to take part in phase 2. Though this response rate may be viewed as low, it is similar to the 16% response rate to the clinician’s questionnaire in the Sinha et al study. Of the 70 responders, 46 identified themselves as clinicians, 16 as clinicians/researchers, 4 as researchers, 1 as a regulatory body member/clinician and 3 as members of industry. After receiving responses from 70 responders, we analysed and collated them. Some answers were very clear and straightforward (eg, diarrhoea duration) while others were unclear and even ambiguous (eg, diet) and it was up to us to either classify the answers into the predefined categories or create new categories. Often, we felt it was appropriate to combine responses into one outcome as well. After collecting and allocating all responses from phase 1 of the clinical questionnaire, the predefined domain/subdomain and outcome classification proved accurate and only a few outcomes needed to be added (see online supplementary table A).

**Parents’ questionnaire results**

Once we received responses from each of the five participating countries, we collated the results and attempted to find those that were most prevalent. A summary of all the results is presented in online supplementary table C.

**Phase 2 Clinical questionnaire results**

A total of 64 responders took part in phase 2 from among ESPGHAN members, ESPID members, researchers, regulatory body members and industry representatives (see online supplementary table D). In the outpatient setting, the need for hospitalisation, diarrhoea duration and dehydration were clearly considered to be the most important outcomes of treatment. In the inpatient setting, on the other hand, hospitalisation duration, diarrhoea duration, dehydration and the use of intravenous rehydration therapy were seen as the most crucial.

**Parents’ questionnaire results**

A total of 32 parents from Belgium, Israel, Italy and Poland were asked to take part in phase 2 (see online supplementary table E). It was found that the most comforting aspects of treatment included the child behaving normally, seeming healthy and being willing to eat and drink, diarrhoea improving and the physician seeing the child and being helpful and informative. The most worrisome aspects of treatment included bloody diarrhoea, fever and the child’s worsening condition.

**DISCUSSION**

**Main findings**

This study aimed to identify outcomes of highest relevance in clinical trials on acute diarrhoea from different perspectives. The first group of responders was represented mainly by clinicians/researchers, but also by the representatives from industry and regulatory people. WG took into account the results of the questionnaires and after a thorough discussion decided on three core outcome sets: two therapeutic core outcome sets for inpatient and outpatient scenarios and a prophylactic core outcome set.

The recommended therapeutic core outcome measures for outpatients include diarrhoea duration, degree of dehydration, need for hospitalisation, proportion of patients recovered by 48 h and adverse effects associated with therapy. The recommended therapeutic core outcome set for inpatients includes diarrhoea duration, degree of dehydration, duration of hospitalisation, proportion of patients recovered by 48 h and adverse effects associated with therapy.

The recommended prophylactic core outcome set includes prevention of diarrhoea, prevention of dehydration, prevention of hospitalisation and adverse effects associated with therapy. WG also discussed that it would be valuable for the core outcome set to include social/life impact outcomes (eg, days of work or kindergarten missed) and economic impact outcomes. However, due to the difficulty in measuring such outcomes, it was decided to delay the introduction of social/life impact

outcomes until further evaluation of these outcomes becomes available. In the meanwhile, these impact outcomes may also be recommended to researchers as a possible additional outcome in nutritional trials.

In contrast to the clinician’s questionnaire, parents had a very different approach. They felt that the child’s health status, including their appearance and behaviour, were of importance. Additionally, the worsening of symptoms and additional worrying symptoms such as bloody diarrhoea or fever were of importance as well. On top of this, staff behaviour was of great importance. The attention, care and approach to the patient by the medical staff (doctors and nurses) were seen as factors that could make the parents very comfortable or very worried, when lacking. It is the opinion of this WG that these results can serve as a best practice guideline to keep in mind when dealing with patients and their families in order to alleviate stress and increase doctor–patient/family cooperation.

Comparison with other studies
Core outcome sets have been implemented in other fields, most notably in rheumatology with Outcome Measures in Rheumatology. This collaboration has designed core outcome sets by reaching consensus among clinicians and researchers on which outcomes merit measuring and also asking patients which outcomes they feel are most important. Core Outcome Measures in Effectiveness Trials (COMET), on the other hand, has brought together researchers interested in developing core outcomes and has collected over 120 published or ongoing studies related to core outcomes, which can be found in the COMET repository (http://www.comet-initiative.org). Although many core outcome sets have been published, there have been none on acute diarrhoea until now.

Study limitations
Our study has some limitations. The Delphi technique in itself is flawed and allows for bias by the collector. However, it is also probably the best method to collect and define such a core outcome set and has been used so in the past.

Low response rate is another potential limitation of our study. Among clinicians, very few initially answered the invitation to phase 1. Those who finally did were asked more directly. This potentially could have resulted in bias. While we did question parents and clinicians for our study, we did not include children. The reason for this is that diarrhoea in children under the age of 5 is a much more worrying condition than in those over 5. As a result, it was this group we focused on. Additionally, it would be very difficult, if not impossible, to gather information on what the <5-year-old patient felt about his treatment, its effects and the outcomes of his treatment.

Moreover, there is always a problem with questionnaires when it comes to comprehension. There is no certainty that those parents who completed the questionnaires in English fully understood what was being asked of them. On top of that, those who answered the translated questionnaires may have been answering questions that were slightly differently translated and thus biased the results. We tried our best to avoid this however.

Finally, a point of concern during preparation for the phase 2 questionnaire was the fact that responses in phase 1 were open to interpretation. They were often unclear, ambiguous or incomprehensible. As a result, they had to be allocated into groups or new groups needed to be created. It cannot be forgotten that this is an area of the study open to bias, mistakes and misinterpretations.

Conclusions and further research
Developing a core outcome set for use in clinical trials is an urgent task. COMMENT and other similar initiatives bring together parties interested in developing standardised sets of outcomes. So far, the COMMENT WG on acute diarrhoea has completed three out of four steps of the project. These included identifying how outcomes related to acute diarrhoea are reported, deciding on the methodology for determining which outcomes to measure in clinical trials and developing a core outcome set for clinical trials performed in subjects with acute diarrhoea. The latter step is being reported in the current paper. To complete the project, WG needs to determine how to measure the outcomes included in the core set. The methodology for this is still under discussion, and this will be the final part of our WG’s task. It would additionally be very useful to ascertain the impact of this core outcome set creation and monitor its implementation in future trials. However, this shall be possible after the completion of step 4 and publishing of the final and complete core outcome set with the core outcome measure set. Of note, the outcome measures that shall be measured and reported in clinical research. As clearly stated by COMET, the outcomes in trials do not need to be restricted to the outcomes in the core set. Instead, the core set should serve as a guide for what should be collected and reported. Thus, core sets make it easier for the results of different trials to be compared, contrasted and combined as is found necessary and useful.

Acknowledgements
Participants who agreed to take part in the Delphi process (for the list, see online supplementary table S, shown with consent from each person).

Collaborators

Contributors
All authors contributed to study design and data collection. J and H developed the first draft of the manuscript. All authors contributed to the development of the final draft of the manuscript. All authors approved the manuscript.

Funding
The workshop that initiated the activity of this working group was supported by the Early Nutrition Academy.

Ethics approval
In order to maintain an ethical approach, no details about patients or families were collected. At the same time all clinicians were asked for their willingness and permission in taking part in the study by answering our questionnaire questions. The Ethics Committee was contacted; no special permission was deemed to be required.

Competing interests
None.

Provenance and peer review
Not commissioned; externally peer reviewed.

REFERENCES


A core outcome set for clinical trials in acute diarrhoea

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CHAPTER 4.
ADHERENCE TO EUROPEAN GUIDELINES FOR ACUTE GASTROENTERITIS

4.1 Rationale and adherence to guidelines for acute gastroenteritis

Acute gastroenteritis (AGE) still is a major cause of medical visit and hospitalization in developed countries being responsible for about 1.5 million outpatient visits and 220,000 hospitalizations per year in USA, before introduction of Rotavirus vaccination [1]. In European children, the estimated annual incidence of AGE ranges from 4% in Sweden to 17% in Germany [2]. In Italy, where the annual incidence of AGE ranges between 4.5% and 19.6% according to age [2,3], the rate of hospital admission for AGE is about 0.8% in pediatric population [3].

In addition to its high incidence, the burden of AGE seems to be related to inappropriate management that results in an excess of hospitalizations, changes in diet and misuse of anti-diarrheal drugs. AGE is a self-limiting, usually mild disease, whose management is in most cases simple and based on consistent and straightforward recommendations. According to most recent available guidelines [4–6] its management basically consists in the replacement of fluids lost through diarrheic stools, vomiting and fever. Anti-diarrheal drugs, changes in diet or laboratory investigations are not routinely needed. In addition to treatment recommendations, selected guidelines also report indications to hospital admission for AGE. However, those recommendations are usually based on experts opinion.

A good compliance to guidelines recommendations for AGE may improve child clinical outcomes, specifically duration of diarrhea and weight gain [7] and reduce its economic burden [8].

However, a low adherence to guidelines recommendations for AGE has been reported both in developed [8,9] and developing countries [10]. Adherence to standard of care for AGE in United States is far from optimal, ranging from 37% in outpatients setting [9] to 69% in hospitalized children [8]. In Italy only 3% of primary-care pediatricians is fully compliant to the evidence-based recommendations, but compliance increases to 65% after a start course on guidelines for AGE [7].

Up to 30% of inappropriate hospital admissions has been reported for other common acute illnesses in children (such as Influenza–like illness) [11], but, to date, no specific data are available on AGE in childhood in Europe.
It should be noted that the National Health Care System in Italy is based on Family Pediatricians, who are in charge of the health of all children. There is no fee for a medical visit in primary care, similarly there is no fee for hospital admission for children.

The aim of this study was to estimate the rate of inappropriate hospital admissions for AGE in children ≤5 years and to assess physician’s compliance with guidelines recommendations for the management of children admitted for AGE.

4.2 Methodology

We carried out a prospective multicenter observational study in collaboration with the Accreditation and Quality Improvement Working Group of the Italian Society of Pediatrics. This national working group involves 126 hospitals admitting children and is aimed at improving the quality of health care delivered to children by the implementation of evidence-based and standardized practice.

All centers involved in this Pediatric Network received an invitation to take part to this prospective study and the instructions for patient enrolment; hospitals that agreed to participate were invited to register at least 5 cases <5 years from November 1st 2011 to June 30th 2012. AGE was defined according to EPSGHAN/ESPID guidelines 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 [5].

Data were recorded by one operator for each hospital at child discharge and loaded into electronic Case Report Form (CRF) available on the pediatric network website (http://networkpediatrico.sip.it/). The CRF included 45 multiple-choice questions grouped in 5 domains (personal and family data, clinical features, home management, reasons for admission and hospital management) (Table 4.1). In addition, the presence of underlying chronic conditions and/or concomitant acute illnesses were recorded in the CRF in order to provide a correct interpretation of outcomes according to patients risk factors.

### Table 4.1. Data reported in the CRF according to each field

<table>
<thead>
<tr>
<th>Fields and contents of the online questionnaire</th>
<th>Personal and family data</th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristic had to be acquired by the pediatrician, comprehending both personal data of the</td>
<td></td>
</tr>
</tbody>
</table>
Home management

Pediatricians were asked to give information on children’s history, especially about diet (free, breast milk, milk-formula, mixed feeding) and the presence of any chronic diseases or concomitant acute illnesses. They were also asked if oral rehydration therapy on patients was already attempted by parents, and if any anti-diarrheal drugs or antibiotics was taken.

Reasons for admission

Every single registered case had to be justified by the pediatrician pointing out the main reasons for admission. They could choose more than one between: severe clinical conditions (to be specified in the following field), inability of the parents to manage the child according to physician’s opinion and explicit request by family.

Clinical features

Children clinical condition at admission was reported. Pediatricians had to specify child weight and the number of diarrheal (1-3;3-5;5-7;>7) and vomiting (1-3; 3-5;>5) episodes per day, characteristics of stools (semi-liquid, watery, soft, bloody), presence of abdominal pain. The grade of dehydration was assessed based on physician’s opinion: state of consciousness (eg. normal, irritable, lethargic), thirst (normal, increased), diuresis (normal, decreased), degree of dehydration in relation with body weight (<5%, 5-9%, >10%), capillary refill time (<2 seconds, 2-3 seconds, >3 seconds), respiratory rate according to age (normal, increased) and skin turgor (immediate retraction, 1-2 seconds, >2 seconds).

Hospital management

Pediatricians were asked to report whether children underwent lab (CBC, CRP, electrolytes, acid-basic equilibrium) and/or microbiological investigations (stool cultures and fecal antigens research); if performed physicians should report the value for some of them (Hb, WBC, CRP, Na+ and HCO3-). Type of rehydration and pharmacological treatment were also recorded. In particular, the rehydration regime (exclusive oral rehydration, IV rehydration <24h or >24h), drug prescriptions (antibiotics, acetorphan/racecadotril, smectite, probiotics, antiemetics) were recorded. Withdrawal of food and any changes in diet or breastfeeding were also to be indicated. Finally, weight at discharge was reported in order to calculate variations and better assess the effect of rehydration therapy and gain of weight.

Outcomes

Primary outcomes were:

1. Appropriateness of hospital admission, based on physicians’ adherence to guidelines criteria for hospitalization

2. Compliance to guidelines for clinical practice in hospitalized children, assessed on physicians’ ability of assessing dehydration, requiring appropriate diagnostic tests and prescribing recommended treatments.

In addition, the number and type of most common violations to guidelines recommendations were considered as secondary outcomes. Outcomes were also analyzed according to geographical area, hospital setting and baseline characteristic or treatment, and risk for prolonged hospitalization.
**Assessment of adherence to guidelines recommendations**

The ESPGHAN/ESPID guidelines [5] were taken as the standard to assess physicians’ compliance to evidence-based recommendations. However, we previously reported that the level of guidelines for AGE is consistently high and the specific recommendations are substantially similar [12]. Adherence to guidelines was assessed with reference to the criteria used by physicians to admit a child with AGE (indications to hospital admission), and prescription and procedures applied during child hospital stay (clinical practice compliance).

**Indications to hospital admission**

The following conditions are reported by ESPGHAN/ESPID guidelines as recommendations for hospital admission [5]:

- Shock
- Severe dehydration (>9% of body weight)
- Neurological abnormalities
- Intractable or bilious vomiting
- ORS treatment failure
- Suspected surgical condition

- Caregivers cannot provide adequate care at home and/or there are social or logistical concerns

The presence of at least one of these conditions was considered as an appropriate indication to admit a child with AGE. Severe clinical conditions, such as shock, suspected surgical conditions and bilious vomiting were always considered appropriate. The other conditions needed to be specifically reported and described by the physician in the CRF to be assessed for appropriateness.

The severity of dehydration was evaluated according to objective clinical signs (capillary refill time, skin turgor etc) and change in child weight. Therefore, estimates reported by physicians and based on child appearance (mildly, moderately, severely dehydrated) were considered unreliable. More specifically, if objective clinical parameters of dehydration did not reflect the grade of dehydration reported by the physician at admission, the hospitalization was defined as “not appropriate” in absence of further indications. Persistent vomiting that leads to oral rehydration failure defines an intractable vomiting episode. Neurological abnormalities, unconsciousness, lethargy and/or seizures are reported by guidelines as specific indications for admission, but isolated crying or irritability not related to clinical signs of dehydration were not considered as adequate criteria of admission.
Logistical concern and inadequacy of family to manage the child at home were considered appropriate criteria only if described in details by physician (eg. distance from the hospital, family not appropriate to manage the child at home).

In addition to these criteria, the explicit request of hospitalization by the family was also considered as a good reason for hospitalization, if supported by physician concern and if details were provided.

**Compliance with clinical practice guidelines**

Once the child was admitted to the hospital, clinical practice compliance to evidence-based recommendations was evaluated based on physicians’ ability to assess dehydration, the need of laboratory investigations and the appropriateness of rehydration regime, nutritional interventions and drug prescriptions.

In details, the following domains were considered for compliance:

1. Evaluation of the main signs/symptoms to assess dehydration (Does the physician report the capillary refill time, skin turgor, respiratory pattern...?)
2. Concordance between the objective assessment of dehydration and physician estimate (Is physician able to adequately assess the reported signs?)
3. Nutritional interventions (eg. withdrawal, changes in diet or feeding)
4. Prescription of blood tests (other than electrolytes)
5. Rehydration route (oral, nasogastric or intravenous)
6. Prescription of stool culture or faecal microbiology
7. Prescription of probiotics (indications and strains)
8. Prescription of antiemetics (indications and drugs)
9. Prescription of antibiotics (indications and drugs)
10. Prescription of anti-diarrheal drugs

The overall compliance was calculated based on the presence of minor and major violations to each of the domains reported above.

A major violation was defined as:
- a medical behavior inconsistent with guidelines recommendations that might negatively affect the course of the disease and/or might be associated with unnecessary costs or inappropriate interventions or any violation to “high grade” recommendations in referral guidelines (strength of...
evidence I and II according to Muir-Gray). An example of major violation was the prescription of not recommended drug or prescription of hydrolyzed formula.

A **minor violations** was defined as:

- a violations that did not substantially change the outcome but was generally considered inappropriate or any violation to “low grade” recommendations in referral guidelines (strength of evidence III, IV and V according to Muir-Gray). An example of minor violation was the prescription of a probiotic strains whose evidence are not conclusive (eg. *Lactobacillus reuteri*) or introduction of an elimination diets (eg. BRAT)

In our model, any major violation reduces the overall compliance of 10% and any minor violation of the 5%; the final score in percentage was calculated by the sum of results reported for each domain (with an ideal maximum of 100%).

We considered full compliance for scores >90% and partial compliance for scores >80%.

A more detailed definition of major and minor violations is reported in the **Table 4.2**. Some cases with peculiar clinical conditions were jointly assessed by all authors.

**Table 4.2. Definition of major and minor violations according to each domain**

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>MAJOR VIOLATION</th>
<th>MINOR VIOLATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of dehydration</td>
<td>Physician does not report any of the signs/symptoms of dehydration: capillary refill time, skin turgor, thirst, respiratory pattern, urinary output, child general appearance</td>
<td>Physician reports less than 50% of reliable signs/symptoms of dehydration (capillary refill should be reported)</td>
</tr>
<tr>
<td>Physician’s estimate of dehydration</td>
<td>/</td>
<td>Physician’s estimate of dehydration at child admission does not reflect the grade of dehydration based on more reliable signs/symptoms</td>
</tr>
</tbody>
</table>
| Nutritional interventions     | - Withdrawal > 6 hours
- Stop breast feeding
- Lactose-free formula
- Cow-milk protein free formula
- Sport drinks                  | Any elimination diet (eg. BRAT diet)                                           |
<p>| Blood tests                   | Do not require electrolytes evaluation in children undergoing blood tests       | Prescription of blood tests other than electrolytes and CBC, CRP in otherwise healthy children |
| Adequacy of rehydration regime| Exclusive oral rehydration in hospitalized children                           | /                                                                               |
| Stool culture and fecal microbiology | /                                   | Stool culture in otherwise healthy children without risk factors or overt bloody diarrhea |</p>
<table>
<thead>
<tr>
<th>Probiotics</th>
<th>Probiotics prescribed but strain or product not reported</th>
<th>-Any probiotic strains different from those recommended by guidelines (LGG and S.boulardii) or -Probiotics for which evidence of efficacy are not conclusive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetics</td>
<td>Antiemetic drugs specifically contraindicated or not considered as appropriate treatment in guidelines (eg. Metoclopramide, Domperidone)</td>
<td>Antiemetic drugs prescribed in absence of intractable or persistent vomiting or when oral rehydration failure was not reported</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Any antibiotic prescribed without a positive culture or a declared risk factor Treatment of non-typhi Salmonella in healthy children</td>
<td>Treatment of Campylobacter &gt; 48-72 hours after the onset of disease</td>
</tr>
<tr>
<td>Anti-diarrheal drugs</td>
<td>All drugs other than those considered as appropriate treatment in guidelines (Smectite, Zinc, Racecadotril/Acetorphan)</td>
<td>/</td>
</tr>
</tbody>
</table>

**Statistical analysis**

The SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA) and R (version 2.5.0; The R Foundation for Statistical Computing) were used for statistical analysis. Analyses included only available data and missing values were not imputed. Data were summarized as means ± standard deviation (95% CI on the mean) for continuous variables and as frequencies (%) for categorical variables. Concordance between subjective (as reported by physicians based on child appearance) and objective (as evaluated by clinical signs, i.e. capillary refill time, skin turgor etc) assessment of the severity of dehydration was based on the unweighted and quadratic weighted Cohen’s kappa statistics.

Univariate and multivariate logistic regression analysis was applied to identify the main factors associated with the following outcomes of interest: inappropriateness of hospital admission, non-compliance with management guidelines, inappropriate medical interventions (prescription of antibiotics, change in diet, microbiological investigation request) and prolonged hospital stay.

For each outcome a different set of potential predictors was chosen based on previous literature and on their known relationship with the outcome. Then, those factors showing a bivariate association with the dependent variable at a p<0.2 were fitted in block in a multivariate logistic regression model. All models were age adjusted regardless of the p value. Associations were expressed as unadjusted and adjusted Odds Ratio with 95% Confidence Intervals (CI).
All significance tests were two-sided with the significance level set at 0.05.

4.3. Results of the national multicenter observational study

Six hundred and twelve children (328 male, mean age 22.8±15.4 months) hospitalized for acute gastroenteritis were enrolled in 31 hospitals. The general characteristics of children and their home management prior to reach the ED are reported in Table 4.3.

Enrolling hospitals were divided in small (15 hospitals) and large (16 hospitals) health-care structures according to the number of available beds for children (less or more than 15) and number of hospitalizations per year (less or more than 1000/year). Most patients were enrolled in non-teaching (433/612) and large hospitals (377/612) (Table 4.3).

Five hundred eighteen children (85%) were hospitalized after a spontaneous access to the emergency department, and only a minority of them was referred to emergency by primary care pediatricians (7%), other hospitals (6%) or domiciliary emergency medical service (2%) before arriving at hospital.

Table 4.3. General characteristics of 612 children hospitalized for acute gastroenteritis

<table>
<thead>
<tr>
<th>General characteristics and home management</th>
<th>328/284</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>328/284</td>
</tr>
<tr>
<td>Mean age(months) ±SD (95%CI)</td>
<td>22.8±15.4 (21.5-24.0)</td>
</tr>
<tr>
<td>Oral rehydration (n/612 and %)</td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>290 (47%)</td>
</tr>
<tr>
<td>- No</td>
<td>85 (14%)</td>
</tr>
<tr>
<td>- Not reported by family</td>
<td>237 (39%)</td>
</tr>
<tr>
<td>Diet (n/612and %)</td>
<td></td>
</tr>
<tr>
<td>- Breast fed children</td>
<td>25 (4%)</td>
</tr>
<tr>
<td>- Formula fed children</td>
<td>69 (11%)</td>
</tr>
<tr>
<td>- Mixed breast feeding children</td>
<td>20 (3%)</td>
</tr>
<tr>
<td>- Weaned children</td>
<td>498 (81%)</td>
</tr>
<tr>
<td>Antidiarrheal drugs prescription (n/612 and %)</td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>76 (13%)</td>
</tr>
<tr>
<td>- No</td>
<td>503 (82%)</td>
</tr>
<tr>
<td>- Not reported by family</td>
<td>33 (5%)</td>
</tr>
<tr>
<td>First medical assessment (n/612 and %)</td>
<td></td>
</tr>
<tr>
<td>- Emergency department</td>
<td>518 (85%)</td>
</tr>
<tr>
<td>- Primary care paediatrician</td>
<td>43 (7%)</td>
</tr>
<tr>
<td>- Other hospital</td>
<td>36 (6%)</td>
</tr>
<tr>
<td>- Emergency medical services</td>
<td>13 (2%)</td>
</tr>
</tbody>
</table>
### Hospital characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean length of stay (days) ± SD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regime of hospitalization (n/612 and % of children)</td>
<td>4.3±2.0 (4.2-4.5)</td>
</tr>
<tr>
<td>- Hospitalization</td>
<td>555 (91%)</td>
</tr>
<tr>
<td>- Emergency department/brief observation</td>
<td>57 (9%)</td>
</tr>
<tr>
<td>Type of hospital (n/612 and % of children)</td>
<td>433 (71%)</td>
</tr>
<tr>
<td>- Non-Teaching hospital</td>
<td>179 (29%)</td>
</tr>
<tr>
<td>Dimension of hospital (n/612 and % of children)</td>
<td>377 (62%)</td>
</tr>
<tr>
<td>- Large (n=16)</td>
<td>235 (38%)</td>
</tr>
</tbody>
</table>

### Clinical conditions and assessment of dehydration

Eighty-eight per cent of children presented with watery (311, 52%) or semi-liquid (212, 36%) stool pattern and 7% reported bloody diarrhea. Vomiting was reported in 79% of patients. About a quarter of children (23%) had another illness together with AGE: 93/612 (15%) were admitted with a concomitant acute illness (in most cases an upper respiratory infection) and other 49/612 (8%) children had an underlying chronic condition (Table 4.4).

### Table 4.4. Clinical conditions at admission to the hospital

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>(n/612 and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes of diarrhoea (n/612 and %)</td>
<td></td>
</tr>
<tr>
<td>- 1-3/day</td>
<td>218 (36%)</td>
</tr>
<tr>
<td>- 3-5/day</td>
<td>205 (33%)</td>
</tr>
<tr>
<td>- 5-7/day</td>
<td>99 (16%)</td>
</tr>
<tr>
<td>- &gt;7/day</td>
<td>90 (15%)</td>
</tr>
<tr>
<td>Stool pattern (n/593 and %)</td>
<td></td>
</tr>
<tr>
<td>- Watery</td>
<td>311 (52%)</td>
</tr>
<tr>
<td>- Semi-liquid</td>
<td>212 (36%)</td>
</tr>
<tr>
<td>- Soft</td>
<td>58 (10%)</td>
</tr>
<tr>
<td>- Solid</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Bloody diarrhoea (n/593 and %)</td>
<td>41 (7%)</td>
</tr>
<tr>
<td>Episodes of vomiting (n/612 and %)</td>
<td></td>
</tr>
<tr>
<td>- No vomiting</td>
<td>129 (21%)</td>
</tr>
<tr>
<td>- 1-3/day</td>
<td>232 (38%)</td>
</tr>
<tr>
<td>- 3-5/day</td>
<td>133 (22%)</td>
</tr>
<tr>
<td>- &gt;5/day</td>
<td>118 (19%)</td>
</tr>
<tr>
<td>Abdominal pain (n/612 and %)</td>
<td>247 (40%)</td>
</tr>
<tr>
<td>Underlying chronic conditions (n/612 and %)</td>
<td>49 (8%)</td>
</tr>
<tr>
<td>Concomitant acute illnesses (n/612 and %)</td>
<td>93 (15%)</td>
</tr>
<tr>
<td>Dehydration parameters</td>
<td></td>
</tr>
<tr>
<td>Capillary refill time. n/612 (%)</td>
<td></td>
</tr>
<tr>
<td>- &lt;2sec</td>
<td>443 (72%)</td>
</tr>
<tr>
<td>- 2-3 sec</td>
<td>96 (16%)</td>
</tr>
<tr>
<td>- &gt;3sec</td>
<td>8 (1%)</td>
</tr>
</tbody>
</table>
Four hundred sixteen patients at admission (68%) were labeled by physician as mildly dehydrated, 165 (27%) showed a moderate dehydration and only 10 (1.6%) as having a severe dehydration or shock (Table 3). However, the objective grade of dehydration evaluated according to the six most reliable clinical signs (Table 4.4), was significantly different from the degree of dehydration estimated by physicians, being 75%, 15% and 1% of children mild, moderate or severely dehydrated, respectively (Table 4.5). The overall concordance between dehydration grade estimated by physicians and the objective assessment was fair and the chance corrected agreement, measured by both un-weighted and weighted kappa, was: 0.30 95%CI (0.39-0.48) and 0.37 95% CI (0.46-0.56), respectively (Table 4.5).

The majority of children (453/612, 74%) underwent IV rehydration. Of those 180 (40%) received IV fluids for less than 24 hours and 273 (60%) for a longer period. Surprisingly a quarter of admitted children (159/612, 25%) received only oral rehydrated during their stay. No child received rehydration through nasogastric tube.

The mean weight gain during hospitalization was only of 60.4 grams (95%CI 22.4-98.5). Only 31 (7%) children gained more than 5% of their body weight compared to that recorded at admission.
Table 4.5. Assessment of dehydration of 612 children admitted for AGE

<table>
<thead>
<tr>
<th>Grade of dehydration</th>
<th>As estimated by physician n (%)</th>
<th>According to clinical dehydration signs n (%)</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observied (%)</td>
</tr>
<tr>
<td>Mild (&lt; 5%)</td>
<td>416 (68%)</td>
<td>457 (75%)</td>
<td>78</td>
</tr>
<tr>
<td>Moderate (5-9%)</td>
<td>165 (27%)</td>
<td>93 (15%)</td>
<td></td>
</tr>
<tr>
<td>Severe (≥ 10%)</td>
<td>10 (1.6%)</td>
<td>5 (1%)</td>
<td></td>
</tr>
<tr>
<td>Not reported/assessable</td>
<td>21 (3.4%)</td>
<td>57 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in weight during hospitalization</th>
<th>Mean+SD (95% CI)</th>
<th>ρ *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at admission (g)</td>
<td>11.077±3.815</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight at discharge (g)</td>
<td>11.138±3.800</td>
<td></td>
</tr>
<tr>
<td>Mean weight gain(g)</td>
<td>60.4±411</td>
<td></td>
</tr>
<tr>
<td>Children who acquired ≥ 5% of weight (n/%)</td>
<td>31/449 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

Concordance was calculated with weighted and unweighted Cohen’s K statistic.

*Significance test is referred to comparison between the weight at admission and discharge

**Appropriateness of hospital admission**

The main reasons for hospital admission were: severe clinical conditions in 438 (73%) children, explicit family request of hospitalization in 98 (16%), and logistical concerns or poor caregivers reliability in 66 (11%) children. Reason for hospital admission was not reported for 10/612 patients.

The majority of hospital admissions (346/602, 57.5%) were inappropriate (Figure 4.1).
Figure 4.1. Appropriate and inappropriate hospital admissions among 612 children with AGE.

Only 188 out of the 438 children who were admitted for severe clinical conditions, as reported by physicians, actually had an indication to hospital admission based on the criteria in guidelines. We considered as appropriate, those cases (66/602) in which physicians declared to admit a child even if his/her clinical conditions did not require hospitalization, but the caregivers could not provide adequate care at home or there were social or logistical concerns that might pose a risk for child health conditions (eg. long distance from the hospital together with mild clinical feature).

Appropriateness of hospital admission was found to be limited to setting and healthcare organization factors (Table 4.6). Appropriateness was greater in small (OR=1.40; 95%CI 1.01-1.95) and teaching hospital (OR=0.68; 95%CI 0.47-1.00). Children arriving at the hospital between 8.00 and 20.00 and/or during the working days run a higher risk of inappropriate admission when compared to those accessing in the weekend (OR=0.6; 95%CI 0.4-0.8) or at night (OR=0.4; 95%CI 0.3-0.7). Those specific risk factors were confirmed both in univariate and multivariate analysis (Table 4.6).

*Compliance with management recommendations during hospital stay.*
Once admitted to the hospital, 2/3 of patients were managed in accordance to evidence-based recommendations, with a mean compliance of 87.63% of medical interventions. More specifically, 21% (126/612) and 45% (274/612) of children were managed in full and partial compliance with guidelines recommendations, respectively (Figure 2).

Table 6. Determinants of inappropriate hospital admissions and compliance to guidelines

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>INAPPROPRIATENESS OF HOSPITAL ADMISSION</strong></td>
<td></td>
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<tr>
<td><strong>DETERMINANTS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hospital dimension (Large vs Small)</td>
<td>1.40 (1.01-1.95)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Type of hospital (Teaching vs Non teaching)</td>
<td>0.68 (0.47-1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Time of admission (20-8 vs 8-20)</td>
<td>0.46 (0.29-0.73)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Admission day (Saturday/Sunday vs Monday/Friday)</td>
<td>0.6 (0.41-0.87)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child age</td>
<td>1.00 (0.99-1.01)</td>
<td>0.288</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First medical assessment</td>
<td></td>
<td>0.555</td>
</tr>
<tr>
<td>- Primary care paediatrician</td>
<td>1</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td>- Other hospital</td>
<td>1.85 (0.74-4.58)</td>
<td>0.182</td>
</tr>
<tr>
<td></td>
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<td>§</td>
</tr>
<tr>
<td>- Emergency department</td>
<td>1.47 (0.79-2.75)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
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<td>§</td>
</tr>
<tr>
<td>- Emergency medical service</td>
<td>1.67 (0.47-5.95)</td>
<td>0.424</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td><strong>NON-COMPLIANCE WITH MANAGEMENT GUIDELINES DURING HOSPITAL STAY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHILD RELATED FACTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99-1.01)</td>
<td>0.898</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying chronic conditions (Yes vs. No)</td>
<td>0.83 (0.44-1.56)</td>
<td>0.570</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td>Concomitant acute illnesses (Yes vs. No)</td>
<td>1.32 (0.84-2.08)</td>
<td>0.228</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td><strong>HEALTH CARE RELATED FACTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital dimension (Large vs Small)</td>
<td>0.95 (0.68-1.35)</td>
<td>0.811</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td>Type of Hospital (Teaching vs Non teaching)</td>
<td>0.69 (0.47-1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasons for admission</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>- Severe clinical conditions</td>
<td>1</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td>- Explicit family request</td>
<td>0.47 (0.28-0.79)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.20 (0.11-0.38)</td>
</tr>
<tr>
<td>- Logistical concerns or poor caregivers reliability</td>
<td>0.31 (0.15-0.60)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 (0.11-0.54)</td>
</tr>
<tr>
<td>Appropriateness of hospital admission (No vs. Yes)</td>
<td>1.29 (0.92-1.81)</td>
<td>0.142</td>
</tr>
</tbody>
</table>
|                                      |                     | 1.55 (1.00-2.39)      | 0.047
**Figure 4.2.** Compliance to guidelines recommendations among children hospitalized for AGE

Note: Compliance was calculated according to the presence of major and/or minor violations committed by physicians during the hospital stay

Most common violations to guidelines are reported on a Pareto Chart in Figure 3. Inappropriate microbiological investigations (404; 35,8%) and nutritional interventions (310, 27,6%) were the two major violations. Anti-diarrheal drugs not included in the guidelines was the third most common violation (271, 24%), with 161 prescriptions of not-indicated probiotics (14,2%), 103 of antibiotics (9,2%) and 7 of other anti-diarrheal drugs (0,6%) (**Figure 4.3**).

**Figure 4.3.** Major violations to guidelines in children hospitalized for AGE.
Children hospitalized in teaching hospitals were more appropriately managed than those in general hospitals (OR=0.59; 95%CI 0.39-0.88). Children who were admitted because of poor family reliability (OR=0.31; 95%CI 0.15-0.60) or based on an explicit family request (OR=0.47; 95%CI 0.28 – 0.79), had a significantly lower risk of being managed inappropriately (p=0.001 and p=0.004, respectively) (Table 4).

Major determinants for the most common violations are reported in Table 4.7.

The presence of more than 5 diarrheal stools was the only feature linked with the request of microbiological investigations (OR=1.66, 95%CI 1.06-2.61). Antibiotics were prescribed more likely in children with bloody diarrhea (OR=3.34, 95%CI 1.51–7.39), in those who showed high value of inflammatory markers (OR=5.9; 95%CI 3.19–10.9), or in those children with concomitant acute illness (OR=3.05;95%CI 1.59-5.83).

The use of antiemetics was higher in children managed in a short observation regimen (7/57) than in those admitted to routine hospitalization (11/555) (11% vs 2% p=0.0006).
### Table 4.7. Determinants of violations and inappropriate medical interventions

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>1.01 [0.99 - 1.03]</td>
<td>1.02 [1.01 - 1.04]</td>
<td>0.99 [0.98 - 1.01]</td>
<td>0.99 [0.98-1]</td>
</tr>
<tr>
<td>N episodes of diarrhea/day</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>0-3 episodes</td>
<td>§</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3-5 episodes</td>
<td>§</td>
<td>1.34 [0.86 - 2.08]</td>
<td>1.47 [0.94 - 2.28]</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 episodes</td>
<td>§</td>
<td>1.48 [0.96 - 2.30]</td>
<td>1.66 [1.06 - 2.61]</td>
<td></td>
</tr>
<tr>
<td>No episodes</td>
<td>§</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1-3 episodes</td>
<td>§</td>
<td>0.44 [0.27 - 0.74]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3-5 episodes</td>
<td>§</td>
<td>0.83 [0.47 - 1.45]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 episodes</td>
<td>§</td>
<td>0.78 [0.44 - 1.40]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Underlying chronic conditions</td>
<td>§</td>
<td>§</td>
<td>-</td>
<td>1.73 [0.84 – 3.56]</td>
</tr>
<tr>
<td>Concomitant acute</td>
<td>3.05 [1.59 - 5.83]</td>
<td>-</td>
<td>0.77 [0.47 - 1.26]</td>
<td>1.80 [1.03 – 3.15]</td>
</tr>
<tr>
<td>Inflammatory markers (high vs. normal)</td>
<td>5.90 [3.19 - 10.9]</td>
<td>&lt;0.001</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>White Blood Count (altered vs. normal)</td>
<td>1.83 [1.07–3.15]</td>
<td>0.064</td>
<td>0.81 [0.53 - 1.24]</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.75 [1.48 – 5.12]</td>
</tr>
<tr>
<td>Probiotics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.66 [1.1 0 – 2.49]</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>§</td>
</tr>
<tr>
<td>Acetorphan</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>§</td>
</tr>
</tbody>
</table>

§ Not entered in the multivariate model (univariate p> 0.2) due to an univariate association
- Not in the set of predictors

**Duration of hospitalization**

The mean length of stay was 4.3±2.0 days, being most children (91%) regularly hospitalized and only a minority (9%) managed in a brief observation regime (Table 4.3).

A hospital stay > 4 days was considered as a prolonged hospitalization, and relative major risk factors were identified (Table 4.7). The presence of other acute clinical conditions together with AGE (OR=1.8 ; 95%CI 1.03–3.15, p=0.04) or episodes of bloody diarrhea (OR=2.83; 95%CI 1.1–7.26; p=0.03) were identified as independent risk factor for prolonged hospital stay. Among treatments, the use of antibiotics (OR=2.75; 95%CI 1.48 – 5.12) and probiotics (OR=1.66 ; 95%CI 1.1 – 2.49)
was significantly associated with prolonged hospitalization (p=0.001; p=0.015, respectively). In contrast, the grade of dehydration and relative characteristics of rehydration were not related to a prolonged stay.

4.4 Discussion

This is the first European prospective study that specifically assesses physicians’ compliance with guidelines recommendations for hospital admissions and management of AGE in children. Our results showed that more than 50% of children with AGE were inappropriately admitted, and, about one third, of those inappropriately admitted, received medical inappropriate interventions during hospital stay in Italy. A similar rate of compliance in hospitalized children with AGE has been recently shown in United States [8].

Physicians’ adherence to standard of care and appropriateness of interventions is a major issue in health [8–10]. Overall, medical behaviors applied in discord with those recommended in evidence-based criteria are strongly related to higher costs and worst clinical outcomes [7,8], but the clinical and economic burden, steadily rises when inappropriateness is related to common diseases such as AGE.

In developed countries, the burden of AGE is still huge because of the high number of hospitalizations, outpatients consultations and medical interventions. A widespread vaccination campaign, as performed in the United States, led to a significant reduction of gastroenteritis-related costs and hospitalizations, by reducing Rotavirus infection episodes in young children [13]. However, the vaccination it is not routinely applied in all countries [14], and even if applied routinely, it is expected to decrease the overall rate of AGE by 25-28% [15].

The assessment of dehydration in children with AGE is the key step for diagnosis and treatment, and drives medical behaviors. According to guidelines the best estimate of AGE severity is the degree of dehydration [5]. The concordance between physicians’ estimate of dehydration grade and the objective assessment was fair, meaning that several physicians overestimated the grade of dehydration. Severe dehydration is the major indication to hospital admission in those children, and variation in weight (at least 5%), if available, is usually reported as the most reliable parameter to assess fluid losses [5]. However, in our population, only a small minority of children underwent a significant weight gain after discharge and the mean weight gain was about 60 grams. Even if during hospitalization some children may experience a weight loss due to lack of
appetite, blood samples and other physical and psychological factors, it’s highly probable that the vast majority of those children was not significantly dehydrated at admission. These findings are confirmed by the objective evaluation of dehydration based on established clinical markers: considering that only 16% of children was moderate-to-severe dehydrated, but 74% underwent IV rehydration (and 273 children for more than 24 hours). A similar discrepancy between guidelines and practice was evident in a previous Canadian study that reported a moderate-to-severe dehydration in only 2% of children with gastroenteritis although 30% of them received intravenous rehydration [16].

Characteristics of health care institutions (teaching vs non-teaching, dimension of institution, location/setting), rather than specific factors related to the child, were the major risk factors for inappropriate hospital admission. A similar high variability in the management of AGE has been reported among different institutions, either in United States or Canada [17,18]. These variations in treatment are not accounted by significant differences in disease prevalence or etiology [8,19]. In addition, it has been demonstrated that an educational intervention focused on guidelines criteria for hospital admission may significantly reduce the number of inappropriate hospital admission for other common pediatric illnesses [11]. This result highlights the importance of medical education and up-dating in determining medical clinical practice.

In our population, an additional determinant of inappropriateness was the hospital access during the daytime in working days. This finding, is similar to that reported in some previous results on admission of children with influenza-like illness [20], and may be related either to the overload in emergency department (ED) during the working days in winter season or also to the availability of beds in the ward. The latter is probably the major determinant for hospital admission, as already proposed in previous study in children with AGE [21]. This pattern may be related to conditions that are typical of winter season, when EDs are characterized by a overwhelming access rate and a little time available for medical decisions, but also to a defensive medicine approach that has been already reported for other common infections in childhood [22].

In Italy, any child up to 16 years is seen for well being visits, vaccinations and management of acute and chronic mild illnesses by primary-care pediatricians who are part of the public Health Care System. Despite this healthcare organization, in our study, the vast majority of children with AGE were admitted after a spontaneous access to the ED, thus skipping the filter of primary care assistance. In addition, considering that the rate of inappropriate admission was similar in children
seen or not seen by primary care pediatricians before reaching the hospital, it seems that there was no “selection” of most severe cases before ED access.

Although the rate of inappropriate hospitalizations was high, once admitted, the mean compliance with guidelines recommendations during their stay was fairly good (66%) and similar to that reported in United States (69%) [8]. Physicians’ compliance was strongly related to the reason of admission: it was better in those patients with no real indications to admission (explicit family request or logistical concerns/poor caregivers reliability). This was probably due to a high consciousness level of not appropriate hospital admission. It could be argued that severity of clinical conditions in inpatients usually induces physicians to exceed in medical interventions in order to avoid any legal issues, feeding the ghost of “defensive medicine”.

Most common violations to guidelines were: inappropriate request of microbiological investigation, nutritional interventions and antibiotic prescriptions. Microbiology is not recommended by guidelines as it has no impact on medical interventions.

Antibiotics were more likely prescribed in children with increased inflammatory markers such as CRP and/or high WBC. However, blood investigations, not routinely recommended by guidelines, are not predictive for a bacterial infection. Some authors proposed a role of CRP as predictor of bacterial etiology, but only very high values (95mg/dl) show a good sensitivity and specificity in children with acute diarrhea [23–25]. In addition, the assumption of antibiotics during hospitalization was strongly related with a prolonged hospital stay and this relation was independent from the presence of concomitant acute illnesses.

Probiotics strains with proved efficacy (Lactobacillus GG and S. boulardii) are currently recommended by guidelines as the first line treatment in addition to ORS [4][5]. In our population, the prescription of probiotic was associated with prolonged hospital stay. However, 70% of prescribed probiotic strains were not those indicated by guidelines as effective.

Although 70% of children experienced vomiting at the onset of AGE, only a minority of patients received antiemetics. The use of antiemetics is a very hot issue in AGE. Recent evidence demonstrates a significant impact of ondansetron in reducing hospitalization as well as the need of IV rehydration in children admitted to ED [26][27]. In our population, antiemetics were more commonly prescribed in emergency department or short observation setting. Discussion among experts is still active on this issue and, even if currently no guidelines recommend the use of ondansetron in routine clinical practice, a larger use in United States and Canada has been reported [26][27].
As previously shown, the significant variability in clinical practice and the lack of adherence to standard of care might be linked to differences in outcomes and health care expenses in industrialized countries [28]. Considering that the cost for a single hospital admission for AGE in Italy is €1300, and that about 50% of hospitalizations are currently inappropriate, we estimated that a full adherence to guidelines recommendations for hospital admission might cut the healthy costs by about €450.000 in our population and that a routine application of standardize care may save about 1 billion of health care expenses related to AGE in Italy.

In conclusion, inappropriate hospital admissions and medical interventions are still common in the management of children with AGE. Major risk factors for inappropriateness are related to physician education and setting rather than to child and disease characteristics. Large quality care improvement process based on local implementation of evidence-based practice may have a huge impact on clinical outcomes and health care costs.
4.5 References


6. National Collaborating Centre for Women’s and Children’s Health (UK) - NICE Clinical Guidelines N 84 Diarrhoea and Vomiting Caused by Gastroenteritis Diagnosis, Assessment and Management in Children Younger than 5 Years 2009.


4.6 Publication

Adherence to Guidelines for Management of Children Hospitalized for Acute Diarrhea

Andrea Lo Vecchio, MD,* Ilaria Liguori, MD,* Dario Bruzzone, PhD,† Riccardo Scotto, MD,* Luciana Parola, MD,‡ Gianluigi Gargantini, MD,§ and Alfredo Guarino, MD§ on behalf of the Accreditation and Quality Improvement Working Group of the Italian Society of Pediatrics§

Background: The major burden of acute gastroenteritis (AGE) in childhood is related to its high frequency and the large number of hospitalizations, medical consultations, tests and drug prescriptions. The adherence to evidence-based recommendations for AGE management in European countries is unknown. The purpose of the study was to compare hospital medical interventions for children admitted for AGE with recommendations reported in the European Societies of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Infectious Diseases guidelines.

Methods: A multicenter prospective study was conducted in 31 Italian hospitals. Data on children were collected through an online clinical reporting form and compared with European Societies of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Infectious Diseases guidelines for AGE. The main outcomes were the inappropriate hospital admissions and the percentage of compliance to the guidelines (full >90%, partial >80% compliance) based on the number and type of violations to evidence-based recommendations.

Results: Six-hundred and twelve children (53.6% male, mean age 22.8 ± 15.4 months) hospitalized for AGE were enrolled. Many hospital admissions (346/602, 57.5%) were inappropriate. Once admitted, 20.6% (126/612) of children were managed in full compliance with the guidelines and 44.7% (274/612) were managed in partial compliance. The most common violations were requests for microbiologic tests (404; 35.8%), diet changes (310; 27.6%) and the prescription of non-recommended probiotics (161; 14.2%), antibiotics (103; 9.2%) and antidiarrheal drugs (53; 4.7%).

Conclusions: Inappropriate hospital admissions and medical interventions are still common in the management of children with AGE in Italy. Implementation of guidelines recommendations is needed to improve quality of care.

Key Words: gastroenteritis, diarrhea, guidelines, adherence, hospital

Acute gastroenteritis (AGE) is a major cause of medical visits and hospitalizations in developed countries and leads to approximately 1.5 million outpatient visits and 220,000 hospitalizations per year in the United States, before the introduction of the Rotavirus vaccine. In Europe, AGE is among the 3 most frequent causes of hospital admission with an estimated annual incidence that ranges between 4% and 17%. In Italy, where the incidence of AGE is slightly higher (between 4.5% and 19.6%), the rate of hospital admission for AGE is about 0.8% in children <5 years.

AGE is a self-limiting and typically mild disease, whose management is, in most cases, simple and based on consistent and straightforward recommendations. According to high quality and authoritative guidelines, the management consists of the replacement of fluids losses. Antidiarrheal drugs, changes in diet or laboratory investigations are not routinely needed. In addition to treatment recommendations, selected guidelines also report the indications for hospital admission for AGE. However, those recommendations are usually based on expert opinion, as there are no controlled trials that specifically study this outcome.

The burden of AGE, mainly related to its high incidence, may be further increased in terms of costs by variability in procedures and excess of medical interventions.

Good compliance to guidelines recommendations for AGE may improve child clinical outcomes and significantly affect the economic burden of the disease by reducing complications and unnecessary interventions.

However, low adherence to guideline recommendations for AGE has been reported both in developed and developing countries. A rate up to 30% of inappropriate hospital admissions has been reported for common acute illnesses in children, such as influenza-like illness, but to date, no specific data are available on AGE in European children.

The aim of this study was to estimate the rate of inappropriate hospital admissions for AGE in children ≤5 years of age and to assess physicians' compliance with guideline recommendations for the management of children admitted for AGE.

PATIENTS AND METHODS

Ethics Statement

This prospective multicenter observational study was approved by the Scientific Committee of the Italian Society of Pediatrics and conducted in close collaboration with the Working Group for the Accreditation and Quality Improvement and the Italian Society of Pediatric Research.

All physicians who agreed to participate in the study and report their practice and prescriptions signed a written informed consent. Each participating institution received a private username and password to access the Pediatric Network website. Any physician might review her/his own data, but did not have access to information recorded by other institutions.

Study Design

The Pediatric Network for the Accreditation and Quality Improvement Working Group is a nationwide network that involves 126 hospitals admitting children (aged <16 years) and is aimed at improving the quality of health care by the promotion of standardized
practice. All centers involved in the Pediatric Network received an invitation to participate in this study. From November 1, 2011, to June 30, 2012, all participating physicians reported their practice about children ≤5 years of age accessing their institution because of AGE. Gastroenteritis was defined according to guidelines developed by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and pediatric infectious diseases (ESPGHAN/ESPDID). Physicians were invited to enroll at least 5 consecutive cases. Data were recorded at the time of discharge by 1 operator for each hospital and loaded into an anonymous electronic case report form available on the pediatric network website (http://network.pediatrico.sip.it; see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/B910).

**Outcomes**

The primary outcomes were as follows:

1. Appropriateness of the hospital admission, based on the specific criteria for hospitalization.
2. Compliance with the indications for the assessment of dehydration, diagnostic tests and recommended treatments in accordance with the guidelines.

In addition, the number and type of violations of the guideline recommendations were considered as secondary outcomes.

**Assessment of Adherence to the Guideline Recommendations**

The evidence-based ESPGHAN/ESPDID guidelines were used as the standard to assess the physicians' compliance to evidence-based recommendations. Adherence to recommendations for admission was assessed by comparing the child's conditions reported by the physician with the criteria of the guidelines. The presence of at least 1 of these conditions was considered as an appropriate indication to admit a child with AGE. Severe clinical conditions, such as shock, suspected surgical conditions and bilious vomiting, were always considered appropriate. The other conditions needed to be specifically described by the physician in the Case Report Form to be checked for appropriateness.

Medical interventions applied during hospital stay, including prescriptions and procedures, were similarly compared with those recommended in the guidelines. The following 10 items were considered to evaluate the appropriateness of medical interventions during hospitalization:

1. Evaluation of the main signs/symptoms to assess dehydration. (Did the physician report the capillary refill time, skin turgor, respiratory pattern, etc.?)
2. Concordance between the objective assessment of dehydration and the physician's estimate. (Was the physician able to adequately assess the reported signs?)
3. Nutritional interventions (eg, withdrawal, changes in diet or feeding)
4. Prescription of blood tests (other than electrolytes)
5. Rehydration route (eg, oral, nasogastric or intravenous)
6. Prescription of microbiological investigations
7. Prescription of probiotics (indications and strains)
8. Prescription of antiemetics (indications and drugs)
9. Prescription of antibiotics (indications and drugs)
10. Prescription of antiarrhythmic drugs

The overall compliance was calculated based on the presence of major and minor violations of each of the domains reported above (see Appendix, Supplemental Digital Content 2, http://links.lww.com/INF/B911).

**A major violation** was defined as follows:

1. A medical intervention inconsistent with guideline recommendations that might negatively affect the course of the disease and/or might be associated with unnecessary costs or inappropriate interventions, or
2. Any violation to "high grade" recommendations in the guidelines (strength of evidence I and II according to the Muir-Gray score).

**A minor violation** was defined as follows:

1. A violation that did not substantially change the outcome but was generally considered inappropriate or any violation to "low grade" recommendations in the referral guidelines (strength of evidence III, IV and V according to Muir-Gray).

In our model, any major violation reduced the overall compliance by 10% and any minor violation by 5%; the final score (percentage) was calculated by the sum of the results reported for each domain, with an ideal maximum of 100%. We considered full compliance for scores >90% and partial compliance for scores >80%.

Chart reviewing and assessment of violations and compliance were independently performed by 3 authors (A.L.V., I.L., and R.S.). Selected cases with peculiar clinical conditions were jointly assessed by all authors and dealt with using the Delphi method.

**Statistical Analysis**

Statistical analysis was performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL) and R (version 2.5.0; The R Foundation for Statistical Computing, Vienna, Austria). Analyses included only available data, and missing values were not imputed:

Data were summarized as means ± SD [95% confidence interval (CI) of the mean] for continuous variables and as frequencies (%) for categorical variables. Concordance between the subjective (as reported by physicians) and objective (as evaluated by clinical signs) assessment of the severity of dehydration was based on the quadratic weighted Cohen's kappa statistics.

Univariate and multivariate logistic regression analysis was applied to identify the main factors associated with inappropriateness of hospital admission, noncompliance with management guidelines and inappropriate medical interventions. Hence, those factors showing a bivariate association with the dependent variable at a level of P < 0.2 were entered en bloc into a multivariate logistic regression model. All models were age-adjusted regardless of the P value. Associations were expressed as unadjusted and adjusted odds ratios (ORs) with 95% CI. All significance tests were 2-sided with the significance level set at 0.05.

**RESULTS**

We enrolled 612 children (328 male, mean age 22.8 ± 15.4 months) hospitalized for AGE in 31 hospitals who agreed to participate to the study. Most were hospitalized (91%, 555/612), whereas 9% (57/612) were managed in a brief observation period consisting of a temporary admission (<12 hours). The mean length of stay was 4.3 ± 2.0 days. The general characteristics of the children and their home management are reported in Table, Supplemental Digital Content 3, http://links.lww.com/INF/B912.

**Clinical Conditions and Assessment of Dehydration**

Eighty-eight percent of the children presented with a watery (371, 52%) or semiliquid (212, 36%) stool pattern and 7% reported
bloody diarrhea. Vomiting was reported in 79% of patients. About a quarter of the children (23%) had another illness together with AGE; of these children, 93/612 (15%) were admitted with a concomitant acute illness, and 49/612 (8%) children had an underlying chronic condition (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B912).

Most patients (416/688) were labeled by the physician as mildly dehydrated, 165 (27%) as moderately dehydrated and only 10 (1.6%) as severely dehydrated or in shock at admission. However, the concordance between physicians’ estimation of dehydration and the objective assessment was poor (weighted kappa 0.37, 95% CI: 0.46–0.56).

Many children (453/612, 74%) underwent IV rehydration. Of these, 180 (40%) received IV fluids for <24 hours and 273 (60%) received fluids for a longer period. A quarter of the children (159/612, 25%) received only oral rehydration. No child received rehydration through a nasogastric tube.

The mean percentage of weight gain during hospitalization, determined as the difference between the weight at discharge and at admission, was 0.66% (95% CI: 0.35–0.97; Table, Supplemental Digital Content 4, http://links.lww.com/INF/B913). Only 31 (7%) children gained >5% of their body weight compared with the weight at admission.

**Appropriate Admission Rates**

The main reported reasons for hospital admission were as follows: severe clinical conditions in 438 (73%) children, an explicit family request for hospitalization in 98 (16%), and logistical concerns or poor reliability of caregivers in 66 (11%) children. No reason for hospital admission was reported for 10/612 patients. Based on the discrepancy with the criteria in the guidelines, many of the hospital admissions (346/610, 57.5%) were inappropriate.

Only 188 out of the 438 children (43%) who were admitted for severe clinical conditions, as reported by the physicians, actually had an indication for hospital admission according to guidelines. We considered as appropriate those cases (66/610, 11%) in which the caregivers could not provide adequate care at home or in which there were social/logistical concerns that might pose a risk for the child’s health conditions. No relevant difference was observed among institutions according to geographical location and type of training (university vs. general hospital). Although, inappropriate hospital admissions were more frequent in large hospitals (>15 beds or 1000 inpatients/yr) than in small institutions (OR: 1.59, 95% CI: 1.04–2.44, P = 0.034).

**Compliance With Recommendations During Hospital Stay**

Once admitted to the hospital, 2/3 of the patients were managed in some agreement with evidence-based recommendations. A total of 21% (126/612) and 45% (274/612) of the children were managed in full or partial compliance with guideline recommendations, respectively (Fig. 1).

No difference in compliance was observed between children managed in a brief observation regimen or regular hospitalization (mean compliance 86.9 ± 9.1 vs. 84.7 ± 9.8, P = 0.37).

Inappropriate requests for microbiological tests (404, 35.8%) and nutritional interventions (310; 27.6%) were the 2 most frequent violations. The administration of antibiologic drugs not included in the guidelines was the third most common violation (271, 24%), with 161 prescriptions for non-indicated probiotics (14.2%), 103 for non-indicated antibiotics (9.2%) and 7 for other non-indicated antibiologic drugs (0.6%).

Children who were admitted because of poor family reliability (OR = 0.31; 95% CI: 0.15–0.60) or based on an explicit request by the caregiver (OR = 0.47; 95% CI: 0.28–0.79) had a significantly lower risk of being managed inappropriately (P = 0.001 and P = 0.004, respectively; Table 1). The major factors associated with the most common violations are reported in Table 2.

The presence of >5 diarrheal stools was the only feature linked with the request for microbiological investigations (OR = 1.66, 95% CI: 1.06–2.61). Antibiotics were prescribed more frequently in children with bloody diarrhea (OR = 3.34, 95% CI: 1.51–7.39), in those who showed increased levels of inflammatory markers (OR = 5.9, 95% CI: 3.19–10.9) and in

**FIGURE 1. Compliance to guideline recommendations among children hospitalized for AGE.**

Note: Compliance was calculated according to the presence of major and/or minor violations committed by physicians during the hospital stay (see Appendix, Supplemental Digital Content 2, http://links.lww.com/INF/B911).
TABLE 1. Determinants of Inappropriate Hospital Admissions and Compliance to Guidelines During Hospitalization

<table>
<thead>
<tr>
<th>Determinants of Inappropriate Admission Rates</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99–1.01)</td>
<td>0.288</td>
</tr>
<tr>
<td>First medical assessment</td>
<td>0.555</td>
<td></td>
</tr>
<tr>
<td>Primary care pediatrician</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other hospital</td>
<td>1.86 (0.74–4.68)</td>
<td>0.182</td>
</tr>
<tr>
<td>Emergency department</td>
<td>1.47 (0.70–2.75)</td>
<td>0.22</td>
</tr>
<tr>
<td>Emergency medical service</td>
<td>1.67 (0.47–6.95)</td>
<td>0.424</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Determinants of noncompliance with guidelines during hospital stay</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99–1.01)</td>
<td>0.898</td>
</tr>
<tr>
<td>Underlying chronic conditions (Yes vs. No)</td>
<td>0.23 (0.44–1.50)</td>
<td>0.87</td>
</tr>
<tr>
<td>Concomitant acute illnesses (Yes vs. No)</td>
<td>1.32 (0.84–2.08)</td>
<td>0.228</td>
</tr>
<tr>
<td>Reasons for admission</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Severe clinical conditions</td>
<td>1</td>
<td>0.047 (0.28–0.79)</td>
</tr>
<tr>
<td>Explicit family request</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistical concerns or poor caregiver reliability</td>
<td>0.31 (0.15–0.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Appropriateness of hospital admission (no vs. yes)</td>
<td>1.29 (0.92–1.81)</td>
<td>0.142</td>
</tr>
</tbody>
</table>

*Net entered in the multivariate model (univariate P > 0.2) because of an univariate association.

those children with a concomitant acute illness (OR = 3.05; 95% CI: 1.59–5.83).

DISCUSSION

This is the first prospective study specifically assessing physicians’ compliance with guideline recommendations for hospital admissions and management of children with AGE. Our results indicate that more than 50% of children with AGE were admitted without meeting the criteria for hospitalization reported in the reference guidelines. Once admitted, about 2/3 of inpatient children were managed in compliance with evidence-based recommendations.

Medical interventions in discordance with evidence-based criteria are strongly associated with higher costs and worse clinical outcomes,13,14 and the clinical and economic burden steadily rises when the inappropriateness is related to common diseases, such as AGE.

In developed countries, the burden of AGE is huge because of the high number of hospitalizations, outpatient consultations and medical interventions. A widespread rotavirus vaccination campaign might significantly reduce costs and hospitalization,15 but it is not applied in all countries,16 and even when routinely applied it is expected to decrease the AGE rate by only 25–28%.17,18

Severe dehydration is the major indication for hospital admission in those children; a weight loss of at least 5% is reported as the most reliable index of dehydration,19 but in our population, only a minority of children experienced a significant weight gain after rehydration. Even if during hospitalization some children might have a weight loss because of lack of appetite, blood samples and other physical and psychological factors, it is highly probable that most children were not significantly dehydrated at admission.

TABLE 2. Factors Associated With Inappropriate Medical Interventions With Prolonged Hospitalization

<table>
<thead>
<tr>
<th>Determinants</th>
<th>Antibiotics</th>
<th>Change in Diet</th>
<th>Stool Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>aOR (95% CI)</td>
<td>P</td>
<td>aOR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (months)</td>
<td>1.01 (0.99–1.05)</td>
<td>0.247</td>
<td>1.02 (1.01–1.04)</td>
</tr>
<tr>
<td>&lt;3 episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3 episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying chronic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant acute illness</td>
<td>3.05 (1.59–5.83)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>3.34 (1.61–7.09)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Inflammatory markers (high vs. normal)</td>
<td>5.09 (2.19–10.09)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>White blood count (altered vs. normal)</td>
<td>1.83 (1.07–3.15)</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Net entered in the multivariate model (univariate P > 0.2) because of an univariate association.

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In our population, although 16% of children were moderately severely dehydrated, about 2/3 underwent IV rehydration. Although the rate of inappropriate admissions was high, the compliance with guidelines in hospitalized children was fairly good (66%) and similar to that reported in United States (69%). Physicians' compliance was strongly related to the reason for admission; compliance was better in those patients with no real indications for admission (explicit family request or poor caregiver reliability). Therefore, there was a trend of not applying excessive invasive interventions in children who were in relatively good clinical condition. The most common violations to the guidelines were inappropriate requests for microbiological investigations, nutritional interventions and antibiotic prescriptions. Microbiological tests are not recommended by the guidelines, unless in specific conditions, as these tests have no impact on medical interventions.

Antibiotics were more likely prescribed in children with signs of inflammation (eg, high C-reactive protein or white blood cells). However, blood tests are not routinely recommended by the guidelines and are not predictive of a bacterial intestinal infection. Although 70% of the children presented with vomiting, only a minority of the patients received antiemetics. The use of antiemetics is a controversial issue in AGE. There is recent consistent evidence that ondansetron may reduce hospitalization and IV rehydration in children who access the emergency department. However, this beneficial effect must be considered in light of concern related to a warning of FDA reporting the association of ondansetron with severe cardiac side effects (FDA: Zofran [ondansetron]: Drug Safety Communication. Risk of Abnormal Heart Rhythms, 2011, from http://www.fda.gov/Safety/MedWatch/SafetyInformation/ SafetyAlertsforHumanMedicalProducts/ucm272041.htm). It should be noted that these severe side effects were reported at doses and routes that differ from those suggested for AGE. Discussion among experts is still active on this issue; currently only 1 guidelines worldwide recommend the use of ondansetron in selected cases, but a large use in the United States and Canada has been reported.2,22

The significant variability in clinical practice and the lack of adherence to the standard of care might be linked to differences in clinical outcomes and health care expenses in industrialized countries. In addition, it has been demonstrated that an educational intervention focused on guidelines may significantly reduce the number of inappropriate hospital admissions for other common pediatric illnesses. This result highlights the importance of medical education and retraining to influence clinical practice.

The main limit of this study was related to the bias of including data reported by physicians. However, the inclusion of a large number of institutions and the identification of a single referent person reporting the interventions of colleagues might have partially reduced this bias. Differently from other studies based on a retrospective analysis of medical prescriptions, our study was the first that has been designed on purpose to prospectively assess medical interventions in a European country.

Inappropriate hospital admissions and medical interventions are still common in the management of children with AGE. Our results are in line with previous findings indicating that effective treatment for AGE is poorly applied by physicians in various European countries and is still far from being optimal even compared with those published >10 years ago.

ACKNOWLEDGMENTS

The authors would like to thank all of our colleagues who, as part of the Accreditation and Quality Improvement Working Group of the Italian Society of Pediatrics, participated in the enrolment of patients. A.L.V., L.P. and G.G., included in the list of authors, had also the responsibility of the enrollment at their respective institutions.

REFERENCES


CHAPTER 5
IMPLEMENTATION OF EFFECTIVE PROBIOTIC STRAINS
FOR THE MANAGEMENT OF CHILDREN HOSPITALIZED
FOR ACUTE GASTROENTERITIS

5.1 Rationale and identification of the clinical problem

Since the introduction of rotavirus vaccine, disease burden due to acute gastroenteritis (AGE), as measured by healthcare utilization and costs, has decreased substantially [1, 2]. However, AGE remains a burden because 1/3 of children under age 3 are still unvaccinated [2]. The mainstay of treatment for AGE has historically been rehydration, which does not reduce the severity or the duration of intestinal symptoms [3]. Probiotics are able to modify the composition of the intestinal microflora, act against enteric pathogens and play an immunomodulatory action, also if a definitive mechanism of action has yet to be defined. A meta-analysis of probiotics for pediatric AGE demonstrated that the probiotic strain *Lactobacillus rhamnosus* GG (LGG) showed a significant reduction in the duration of diarrhea and risk of diarrhea lasting more than 7 days [4]. Evidence-based guidelines produced in developed countries identify LGG as a valid and effective adjunct to oral rehydration solution for the treatment of AGE [5-7].

Adherence to standard of care for AGE in United States is far from optimal [8]. A recent survey on North American physicians practicing pediatric emergency medicine reported a prescription of Probiotics in only 15% of children with AGE in Canada and United states [9]. About 70% of those physicians working in United States referred that a better knowledge of high quality probiotic strains available in USA would increase the likelihood of their recommendation, and that the absence of a clinical trial conducted in North America represented the main barrier for prescription.

5.2 Evidence in support to the use of *Lactobacillus rhamnosus* GG for the treatment of children hospitalized for acute diarrhea
Acute gastroenteritis is probably the main, certainly the original field of application for probiotics. A large number of data have been obtained since the paper that firstly provided relevant evidence for the efficacy of *Lactobacillus rhamnosus* GG (LGG) in the treatment of AGE [10].

In the last years, an increasing number of RCTs have been published on this issue in various settings and with different outcomes. However, the data available are progressively merging in providing compelling indications that probiotic administration is effective against AGE.

From a review of guidelines available worldwide, six produced either in developed or developing countries consider the use of probiotic as a therapeutic option in addition to rehydration [6, 11, 12, 13, 14, 15].

LGG is the most studied strain and, as a consequence, has obtained consistent evidence of efficacy. All the documents including probiotics in their recommendations, consider LGG as the main intervention based on clinical evidence. There is “conclusive” evidence that GG reduces the severity and duration of diarrhea in multiple conditions.

The recommendation slightly varies among different guidelines according to the setting and the availability of products on the market. As an example, in Australia, although evidence support the use of LGG no probiotics are available.

Two authoritative documents have been developed in 2014 by the ESPGHAN, one is a position paper that specifically addresses the use of probiotics in children with AGE [16] and the other is a more complete document on the overall management of AGE in children [11]. Those documents provide clear-cut recommendations. Recommendations were provided only if at least two distinct RCTs were available. Briefly, according to published data, selected probiotic reduce the severity and duration of symptoms by approximately 24 hours (without substantial differences in efficacy among effective strains), and the risk of complications.

A total of 4 strains were recommended for active treatment of gastroenteritis, in adjunct to oral rehydration therapy. However, LGG that was “strongly recommended”, was the only one that received a similar recommendation in 2008 version of guidelines [5].

Though LGG has primarily been studied in preschool children, it has been tested in children older than 5 years and in adults [17], with similar results as that for younger children [18]. Considering the available evidence and the safety profile of probiotics, the recommendation for use of LGG as treatment for acute diarrhea can be generalized to include older children.
A recent meta-analysis [19] of 11 RCTs involving 2444 children with acute infectious diarrhea found that LGG is associated with a significant reduction in diarrhea duration (mean difference, MD -1.05 days, 95% CI -1.7 to -0.4), LGG was effective in children treated in Europe (five RCTs, n = 744, MD -1.27 days, 95% CI -2.04 to -0.49); in the non-European setting, the difference between the LGG group and the control group was of a borderline statistical significance (six RCTs, n = 1700, MD -0.87, 95% CI -1.81 to 0.08).

A previous meta-analysis reported a reduction in the risk of diarrhea longer than 7 days (1 RCT, Relative Risk (RR): 0.25, 95% CI: 0.09 to 0.75), and duration of hospitalization (3 RCTs, number of participants =535; WMD -0.58, 95% CI: -0.8 to -0.4) [4].

**Dose-dependent effect**

The specific dose of probiotics is still an issue. Specifically for the treatment of AGE, strong evidence supported a dose-related effect, being high doses of LGG (> 1010 CFUs/day) (eight RCTs, n = 1488, MD -1.11 days, 95% CI -1.91 to -0.31) more effective than low doses in reducing the duration of diarrhea (three RCTs, n = 956, MD -0.9 day, 95% CI -2.5 to 0.69) [19].

Since the demonstration of a significant reduction of Rotavirus shedding in stools in children receiving *Lactobacillus rhamnosus* [10], and the following evidence of a dose-dependent effect [20], other documents reported that probiotics overall seems to have a stronger effect in Rotavirus-positive diarrhea rather than in other etiology. It should be considered that the spreading of Rotavirus immunization might change in part the current scenario.

**Health benefits**

The health benefits for LGG administration in adjunct to ORS consist of reduction of diarrhea duration, reduction in risk of having a protracted diarrhea and reduction of duration of hospitalization.

Indirectly, the use of LGG could lead to a reduction of AGE-related costs in term of work days lost by the family and days of hospitalization; and the routine use of LGG in inpatients and community children with acute diarrhea could reduce the exposure to nosocomial and daycare infection.
5.3 Intervention to implement the use of *Lactobacillus rhamnosus* GG in a tertiary care children hospital

In 2005, and again in 2011, the Cincinnati Children Hospital Medical Center in Ohio, United States developed an evidence-based Clinical Practice Guideline, which recommended consideration of probiotic use in patients with AGE [21]. Despite the evidence and local recommendations, only 1% of AGE patients admitted to our general pediatric service were prescribed probiotics.

**Aims of the study**

The aim of this study was to increase the prescription of *Lactobacillus GG* at admission from 1% to 90% within 120 days for children hospitalized on a general pediatric service with a diagnosis of AGE.

**Methods**

*Setting*

Cincinnati Children’s Hospital Medical Center (CCHMC) is a large, urban pediatric academic medical center located in the Midwest United States, which uses an electronic medical record (EMR) for all inpatients. In fiscal year 2011, CCHMC had 528 registered inpatient beds of which 200 were patients admitted with the diagnosis of AGE. Patients admitted to the general pediatric service are admitted at the main campus and a satellite community campus. At the main hospital, care is provided by teams of residents and medical students that are supervised by CCHMC pediatric hospitalists for 85% of the patients and community-based pediatricians for 15% of the patients. Approximately 160 medical students and residents receive clinical training annually on the general pediatric service. This quality improvement initiative took place on three general pediatric inpatient units, two at the main campus and one at the satellite location.

*Planning the Intervention*

A CCHMC general pediatric hospitalist attending physician led a multidisciplinary team which included other hospital medicine attending physicians, a visiting pediatrician, a research
The team used a Rapid Cycle Improvement Collaborative (RCIC) [11] at CCHMC to achieve the goal of increasing probiotic prescription on admission within a 120-day period. This involved group learning sessions over 4 months with didactic presentations and structured group activities to learn the Model for Improvement [23] and apply Quality Improvement (QI) methods to achieve an improvement goal. The team mapped the existing AGE admission process, conducted a failure mode effects analysis [24], and identified key drivers of LGG use, and developed interventions to promote LGG use. Figure 5.1 depicts the final key driver diagram.

Figure 5.1. Key drivers diagram

The team developed a SMART aim that was specific, measureable, actionable, relevant, and time-bound, to increase the prescription rate of LGG at admission from 1% to >90% within 120 days for children hospitalized on the general pediatric service with a diagnosis of AGE. Patients considered for inclusion were between 2 months and 18 years old admitted to the general pediatric service with the diagnosis of AGE. Acute Gastroenteritis was defined as a decrease in stool consistency and/or an increase in frequency of evacuations with 3 or more stools in the preceding 24 hour period, with or without vomiting or fever. Patients with complex medical conditions or with presumed bacterial gastroenteritis were excluded.
**Improvement Activities**

Interventions focused on 4 main areas to address the key drivers identified. The interventions were tested through Plan-Do-Study-Act (PDSA) cycles [23] on three general medical units and adapted as needed.

**Education**

- In April 2011, the improvement team presented the evidence for LGG to residents and medical students at a morning conference and to the general pediatric attending physicians at a regularly scheduled section meeting. Participants completed pre- and post- assessment surveys on their knowledge and practice of the evidence that LGG, when administered to children with AGE, shortens the course of acute and protracted diarrhea. Nursing staff on the general pediatric units were informed of this same information by the nursing leadership. A second educational session was given in July 2011 to teach the incoming residents and to remind the existing residents about probiotics and AGE.

- To spread knowledge of the evidence and the team’s improvement efforts, several means of communication were used to reach out to community physicians and other members of the CCHMC community. A one-page flyer summarizing the evidence and implementation project was disseminated to physician practices by CCHMC representatives who serve as liaisons between the hospital and community-based practices. A paragraph on the evidence and the LGG project was also posted on the CCHMC internal website and included in an institution-wide staff bulletin distributed to medical staff. Contact information for the team leader and a web link to our institutional Best Evidence Statement [25], which summarizes the evidence for use of LGG in children with diarrhea, were included on all materials.

- To further remind residents and also capture visiting residents and medical students who were unfamiliar with the project, a member of the improvement team attended the monthly general pediatric team orientation meeting to provide a very brief reminder. Relevant information regarding eligibility criteria and dosage information was posted in the team rooms and on the resident website. Several months into the project, the residency program migrated to shift based scheduling to address new Accreditation Council for Graduate Medical Education (ACGME) work hour restrictions, which meant residents working the night shift were not able to attend the team orientation meeting. To educate the night shift residents,
two slides summarizing the LGG project were delivered during their existing weekly evening educational sessions.

**Feedback on Performance**
Updated run charts were posted in both resident team rooms and attending workrooms to provide feedback for the medical team.

**Pharmacy**
In April 2011, to address the problem that LGG not available at the satellite campus’ inpatient pharmacy, the satellite pharmacy partnered with our group and began to stock LGG.

**Order set**
To incorporate a higher reliability intervention,[26, 27] the team worked with an EMR system specialist to update the existing gastroenteritis order set to include a hyperlink to the Best Evidence Statement and an order that defaulted to the prescription of LGG specifying the appropriate dose and schedule of administration.

**Identify and mitigate**
A research assistant reviewed the EMR each weekday to identify eligible patients with AGE. To prevent failures, the research assistant notified the attending physician and residents responsible for the patient’s care by email when an eligible patient was identified who did not have LGG ordered. The email notification included a reminder of the LGG project aim, evidence for LGG use in AGE patients and information on the appropriate dosage and timing of administration. This weekday mitigation strategy was designed to remind the team in semi-real time so they could prescribe LGG if they deemed medically appropriate.

**Methods of Evaluation**
Pre intervention data was collected through manual chart review of all patients discharged from the general pediatrics service between January 1, 2011 and April 3, 2011. Post intervention data were obtained through a daily scan of general pediatrics patients and manual chart review of eligible patients admitted between April 4, 2011 and January 22, 2012. A research assistant trained in data collection and interpretation reviewed the list of hospital
medical patients each weekday, searching the problem list and chief complaint for the following keywords: acute gastroenteritis, diarrhea, dehydration, or vomiting, to identify eligible patients. On Monday morning, the research assistant would also review patients admitted during the weekend. Once a patient had been identified, the research assistant noted whether the patient met the inclusion criteria for the QI project. The eligibility of patients of questionable inclusion/exclusion status was determined by consensus after the case was reviewed with at least two physicians on the improvement team. Prescription of LGG at admission was defined as LGG being ordered for an eligible patient within 18 hours of admission, regardless of whether the team received a reminder.

**Analysis**

The research assistant recorded data and created run charts using Microsoft Excel®. Run charts [28] display data in a timed sequence and help detect special causes of variation. Run charts were updated weekly to reflect the percentage of eligible patients receiving LGG at the main campus, satellite campus, and both locations combined.

**5.4 Results of the rapid implementation program**

Prescription of LGG at admission for children with AGE increased from 1% to 100% within 6 weeks of beginning the project (**Figure 5.2**).

The educational sessions for attending physicians, residents, and medical students were an effective method of knowledge transfer. After the sessions, participants were more knowledgeable that probiotics reduce the duration of diarrhea in a dose dependent fashion and were more likely to prescribe probiotics (Table A).

Three failures accrued soon after the new interns started in July 2011. Subsequently, prescription of LGG at admission has been sustained for the past 6 months.

As expected, our average length of stay did not change as a result of our interventions (Table B).

**Table 5.1. Survey of Practitioners’ Knowledge about probiotics and current or planned prescribing habits**
<table>
<thead>
<tr>
<th></th>
<th>Before Probiotic Education</th>
<th>After Probiotic Education</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I typically treat children with AGE with probiotics.</td>
<td>% agreement</td>
<td>% agreement</td>
<td>.001</td>
</tr>
<tr>
<td>Residents or medical students (n = 30)</td>
<td>0</td>
<td>80</td>
<td>.001</td>
</tr>
<tr>
<td>Hospital medicine attending physicians (n = 11)</td>
<td>18</td>
<td>63</td>
<td>.001</td>
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<tr>
<td>The evidence supports probiotics’ reduction of diarrhea.</td>
<td>% correct</td>
<td>% correct</td>
<td>.001</td>
</tr>
<tr>
<td>Residents or medical students (n = 30)</td>
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<td>.001</td>
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<td>Hospital medicine attending physicians (n = 11)</td>
<td>70</td>
<td>100</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Probiotics have a dose-dependent efficacy.</td>
<td>% correct</td>
<td>% correct</td>
<td>.001</td>
</tr>
<tr>
<td>Residents or medical students (n = 30)</td>
<td>59</td>
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<td>.001</td>
</tr>
<tr>
<td>Hospital medicine attending physicians (n = 11)</td>
<td>70</td>
<td>100</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Figure 5.2. Run chart of the prescription of LGG in children admitted to CCHMC for AGE

Conclusions

The rapid implementation of evidence-based practice is possible when utilizing improvement science methods. Keys to the success of our specific project were interdisciplinary collaboration, use of an electronic medical record, and identification and mitigation of failures.
5.5 References


12. Acute Gastroenteritis Guideline Team, Cincinnati Children's Hospital Medical Center: Evidence- based care guideline for prevention and management of acute gastroenteritis in


5.6 Publications

   Rapid adoption of Lactobacillus rhamnosus GG for Acute gastroenteritis.
   *Pediatrics* 2013;131:S96


   Probiotics for prevention and treatment of diarrhea.
   *Journal Clinical Gastroenterology* 2015 – accepted for publication
Rapid Adoption of *Lactobacillus rhamnosus* GG for Acute Gastroenteritis

**abstract**

**BACKGROUND AND OBJECTIVES:** A 2007 meta-analysis showed probiotics, specifically *Lactobacillus rhamnosus* GG (LGG), shorten diarrhea from acute gastroenteritis (AGE) by 24 hours and decrease risk of progression beyond 7 days. In 2005, our institution published a guideline recommending consideration of probiotics for patients with AGE, but only 1% of inpatients with AGE were prescribed LGG. The objective of this study was to increase inpatient prescribing of LGG at admission to >90%, for children hospitalized with AGE, within 120 days.

**METHODS:** This quality improvement study included patients aged 2 months to 18 years admitted to general pediatrics with AGE and diarrhea. Diarrhea was defined as looser or ≥3 stools in the preceding 24 hours. Patients with complex medical conditions or with presumed bacterial gastroenteritis were excluded. Admitting and supervising clinicians were educated on the evidence. We ensured LGG was adequately stocked in our pharmacies and updated an AGE-specific computerized order set to include a default LGG order. Failure identification and mitigation were conducted via daily electronic chart review and e-mail communication. Primary outcome was the percentage of included patients prescribed LGG within 18 hours of admission. Intervention impact was assessed with run charts tracking our primary outcome over time.

**RESULTS:** The prescribing rate increased to 100% within 6 weeks and has been sustained for 7 months.

**CONCLUSIONS:** Keys to success were pharmacy collaboration, use of an electronic medical record for a standardized order set, and rapid identification and mitigation of failures. Rapid implementation of evidence-based practices is possible using improvement science methods. *Pediatrics* 2015;131:996–S102.

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**KEY WORDS**
evidence-based practice, gastroenteritis, probiotics, quality improvement, diarrhea, *Lactobacillus rhamnosus* GG

**ABBREVIATIONS**
AGE—acute gastroenteritis
CCHMC—Cincinnati Children’s Hospital Medical Center
EMR—electronic medical record
LGG—*Lactobacillus rhamnosus* GG
QI—quality improvement

Drs Parker, Schaffzin, Lo Vecchio, Simmons, and Ms You, Vanderhaar, Gerhardt contributed to the acquisition of data. Drs Parker, Schaffzin, Lo Vecchio, Guzd, Brinkman, White, Simmons, and Ms You, Vanderhaar, Gerhardt drafted the manuscript. All authors are responsible for the reported research, participated in the concept and design, analysis and interpretation of data, drafting and revising of the manuscript, contributed to the critical revision of the manuscript for important intellectual content, and approved the manuscript as submitted.

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Since the introduction of the rotavirus vaccine, disease burden attributable to acute gastroenteritis (AGE), as measured by health care utilization and costs, has decreased substantially.\textsuperscript{1,2} However, AGE remains a health care burden because of the approximately one-third of children younger than 3 who are unvaccinated\textsuperscript{2} or infected with other viruses.\textsuperscript{3}

The mainstay treatment of AGE historically has been rehydration, which does not reduce the severity or duration of intestinal symptoms.\textsuperscript{4} A meta-analysis of the use of probiotics for pediatric AGE demonstrated that the probiotic strain \textit{Lactobacillus rhamnosus} GG (LGG) showed significant reductions in the duration of diarrhea and risk of diarrhea lasting 7 days.\textsuperscript{5} Evidence-based guidelines produced in developed countries identify LGG as a valid and effective adjunct to oral rehydration for the treatment of AGE, as does a recent American Academy of Pediatrics clinical report.\textsuperscript{6-9} Adherence to one such guideline demonstrated shortened diarrhea and improved weight gain among children with AGE.\textsuperscript{10} Cincinnati Children’s Hospital Medical Center (CCHMC) has developed evidence-based guidelines for 15 years. In 2005, our institution updated an evidence-based clinical practice guideline that recommended consideration of probiotic use for patients with AGE.\textsuperscript{11} Despite the evidence and local recommendation, only 1% of patients with AGE admitted to general pediatrics were prescribed probiotics.

The aim of this study was to increase the percentage of children with AGE admitted to general pediatrics who received LGG from 1% to 80% within 120 days.

**METHODS**

**Setting**

CCHMC is a large, urban pediatric academic medical center that uses an electronic medical record (EMR). In fiscal year 2011, CCHMC had 200 patients admitted to general pediatrics with the diagnosis of AGE. Patients admitted to the general pediatric service are admitted at the main campus and a satellite community campus. At the main hospital, care is provided by teams of residents and medical students who are supervised by CCHMC pediatric hospitalists for 85% of the patients and community-based pediatricians for the remaining 15%. Approximately 150 medical students and 180 pediatric residents receive clinical training annually on the main hospital general pediatric service. Care at the satellite community campus is almost exclusively given by attending physicians. This quality improvement (QI) initiative took place on 3 general pediatric inpatient units: 2 at the main campus and 1 at the satellite location.

**Planning the Intervention**

One CCHMC pediatric hospitalist attending physician and a visiting pediatrician co-led a multidisciplinary team that included other hospital medicine attending physicians, a research assistant, physician and nurse representatives of the evidence-based guideline development group, and a QI coach. The team used a Rapid Cycle Improvement Collaborative\textsuperscript{12} at CCHMC, which involved 7 group learning sessions over 4 months to learn the Model for Improvement\textsuperscript{13} and apply QI methods to achieve an improvement goal. The team met approximately weekly in the initial phase of the project to gauge progress and plan interventions. The team mapped the existing AGE admission process, conducted a failure mode effects analysis,\textsuperscript{14} identified key drivers of LGG use, and developed interventions to promote LGG use. Figure 1 depicts the final key driver diagram. Patients considered for inclusion were between 2 months and 18 years old and admitted to the general pediatric service with the diagnosis of AGE with diarrhea. Compliant with the World Health Organization definition, diarrhea was defined as decreased stool consistency or 3 or more stools in the preceding 24-hour period. Patients with complex comorbid conditions or with presumed bacterial gastroenteritis, such as patients presenting with bloody diarrhea, were excluded.

**Improvement Activities**

Interventions focused on 4 main areas to address the key drivers identified a priori. The interventions were tested through Plan-Do-Study-Act cycles.\textsuperscript{15}

**Education**

- In April 2011, the improvement team presented the evidence for LGG to residents and medical students at a morning conference and to the hospitalist attending physicians at a regularly scheduled meeting. At the session, participants completed pre- and post-assessment surveys on their knowledge and practice of the evidence that LGG, when administered to children with AGE, shortens the course of acute and protracted diarrhea. Nursing staff on the general units were informed of this same information by nursing leadership. A second educational session was given in July 2011 to teach the incoming residents and remind the existing residents about probiotics and AGE.

- To spread knowledge of the evidence and the improvement efforts, several means of communication were used to reach out to community physicians and other members of the CCHMC community. A 1-page flyer summarizing the evidence and implementation project was disseminated by CCHMC representatives who serve as liaisons between the hospital and community-based practices. A paragraph on the evidence and the QI project was also posted...
on the CCHMC internal Web site and included in an institution-wide bulletin distributed to medical staff. Contact information for the team leaders and a Web link to our institutional Best Evidence Statement, which summarizes the evidence for use of LGG in children with diarrhea, were included on all materials.

To further remind residents and orient visiting residents and medical students to the project, a member of the improvement team attended the monthly general pediatriic team orientation meeting to provide feedback on performance.

Pharmacy

- In April 2011, our improvement group partnered with pharmacy to ensure LGG was available in an adequate dose of $10^{10}$ colony-forming units per capsule, and was stocked at both the main and satellite locations, as it had previously only been stocked at the main location.

Order Set

- To incorporate a higher reliability intervention, the team worked with an EMR system specialist to update the existing gastroenteritis order set to include a hyperlink to the Best Evidence Statement and an order that defaulted to the prescription of LGG specifying the appropriate dose and schedule of administration. Practitioners choosing the AGE order set needed to delete the order for LGG to not prescribe LGG.

Identify and Mitigate

- A research assistant reviewed the EMR each weekday to identify eligible patients with AGE. To prevent failures, the research assistant notified the attending physician and residents responsible for the patient’s care by e-mail when an eligible patient was identified who did not have LGG ordered. The e-mail notification included a reminder of the LGG project aim, evidence for LGG use in patients with AGE, and information on the appropriate dosage and timing of administration. This mitigation strategy was designed to remind the team so they could prescribe LGG if deemed medically appropriate and also to reinforce the practice change. These e-mail notifications were recently discontinued in an effort to scale down improvement efforts.

Methods of Evaluation

Preintervention data were collected through manual chart review of all patients discharged from the general pediatrics service between January 1 and April 3, 2011. Postintervention data were obtained through a daily manual electronic chart review of eligible patients admitted between April 4, 2011, and February 26, 2012. To identify eligible patients, a research assistant trained in data collection and interpretation reviewed the list of general pediatrics patients each weekday, searching the problem list created by the admitting team for the following keywords: acute gastroenteritis, diarrhea, dehydration, or vomiting. Each Monday morning, the research assistant also reviewed patients admitted during the weekend. Once a patient was identified, the research assistant reviewed the medical record and applied inclusion and exclusion criteria and case definitions to determine eligibility. When eligibility was uncertain, the case was reviewed with at least 2 physicians on the improvement team to reach consensus. Prescription of LGG at admission was defined as LGG being ordered for an eligible patient within 18
hours of admission, regardless of whether the team received a reminder.

**Analysis**

Pre-and post-assessment data from educational sessions were analyzed by using a χ² test to calculate values for statistical significance. The research assistant recorded performance data and created run charts using Microsoft Excel (Microsoft, Redmond, WA). Run charts were updated weekly to reflect the percentage of eligible patients receiving LGG, and displayed data in a timed sequence to help detect special causes of variation.15

**Human Subject Protection**

The CCHMC institutional review board reviewed the project and considered it to be a local QI initiative and not research involving human subjects. Informed consent beyond the standard consent for treatment of all inpatients was not required.

**RESULTS**

Pre- and postassessment surveys for the attending physicians, residents, and medical students on their LGG knowledge demonstrated that the educational sessions significantly improved knowledge of LGG efficacy and improved their likelihood to prescribe probiotics (Table 1). Prescription of LGG at admission for children with AGE increased from 1% to 100% within 6 weeks of beginning the project (Fig 2). Three failures occurred soon after the new interns started in July 2011. Subsequently, prescribing of LGG at admission has been sustained for the past 7 months at 100%. The percentage of eligible patients requiring real-time e-mail mitigation had declined since the early phases of the project (Fig 3).

**DISCUSSION**

We used improvement science and reliability methods17 to successfully implement an evidence-based practice change within 6 weeks that has been sustained for >7 months. Improvement science is the application of the scientific method to improve health care delivery systems.15,19 Historically, practice change that adopts evidence-based recommendations is a slow process, taking on average 17 years for research to be translated into practice.20 Our Hospital Medicine division has had similar success with changing practice related to hand hygiene21,22 and rapid adoption of evidence to change practice regarding the treatment of osteomyelitis.23 We propose that rapid and sustainable evidence-based practice change can be achieved by applying improvement science methods.

Education is often the first step in any change process; however, education and training are low reliability interventions when used alone.17 Thus, a successful change initiative must include additional strategies to achieve sustainability. In our project, we used education to develop consensus for the practice change, to ensure that physicians and nurses understood the potential risks and benefits of LGG, and to establish the foundation for subsequent interventions. We learned from our failures in July that given the frequent change of care providers within an academic setting, repetition of education was essential; however, as the message spread among our care teams, less formalized, more concise education proved effective.

Key partnerships within our institution led to interventions incorporating higher reliability interventions that helped us to achieve our goal. The inpatient pharmacy took steps to ensure that LGG was available in the correct formulation at both inpatient sites. EMR analysts modified an existing order set to include LGG as the default order at the correct dose. In addition to facilitating LGG ordering, the EMR afforded us the ability to identify eligible patients quickly. Once identified, near real-time mitigation of failures in LGG ordering helped to increase our success, especially during the initial weeks of the project. This project leveraged the existing relationships, the value of evidence-based practice, and the culture of QI that exists within our institution. However, we do not believe that such efforts are limited to facilities with an existing QI framework, as optimized care delivery based on evidence is a universal concept.

There are some limitations to our rapid implementation project. Because the volume of patients admitted from week to week was small, we cannot say if the methods are generalizable to high-volume conditions. Reliable delivery of evidence-based care may require different interventions when addressing low-versus-high-volume conditions.

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**TABLE 1** Survey of Practitioners’ Knowledge About Probiotics and Current or Planned Prescribing Habits

<table>
<thead>
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<td>I typically treat children with AGE with probiotics</td>
<td>% agreement</td>
<td>% agreement</td>
<td>.001</td>
</tr>
<tr>
<td>Residents or medical students (n = 50)</td>
<td>0</td>
<td>80</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital medicine attending physicians (n = 11)</td>
<td>19</td>
<td>63</td>
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<td>70</td>
<td>100</td>
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<td>70</td>
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<td>&lt;.001</td>
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</tbody>
</table>
Because the purpose of the project was to create a framework for evidence-based practice implementation based on a target with a solid foundation of evidence for efficacy with minimal harm, LGG for use in children with AGE was an excellent place to start. Although no staff were added as a result of our project, the effort was relatively great, involving research assistant, physician, and pharmacist time. In our experience, chart review and identification and mitigation need not be conducted by a research assistant. With the proper training, a resident, medical student, or administrative assistant would be able to complete the task with relatively minimal physician or pharmacist oversight. Our next steps include further decreasing the labor required to sustain our system.

**Percentage of Patients Receiving E-mail Reminder for LGG Prescribing**

![Run chart of percentage of patients requiring e-mail reminder for prescribing.](image)

**Figure 3**

Run chart of percentage of patients requiring e-mail reminder for prescribing.
This will include automation of eligible patient identification using the EMR and switching to a retrospective review process, as recent performance has been sustained with sufficiently minimal need to identify and mitigate (Fig 3), which allowed this effort to be discontinued with maintained success.

A second limitation of our study is our reliance on documentation in the EMR (e.g. diagnosis in problem list) to identify eligible patients. Chart review has been shown to improve the positive predictive value of case identification using International Classification of Diseases, Ninth Revision codes, but still achieved only an 85% positive predictive value in 1 study.24 Thus, we may not have identified all eligible patients.

To limit this as a potential for bias, we used a single trained reviewer who used a standardized approach to identify eligible patients and collect patient data. Additionally, when the reviewer was unsure whether to include or exclude a patient, we used a consensus process to guard against misclassification.

The finding of a low baseline prescription rate in the face of extensive evidence and local recommendation was somewhat surprising, but this same practice pattern has been noted among the international pediatric gastroenterology community.25 As we disseminated our education, we discovered a number of barriers that may have contributed to this phenomenon. First, we were not able to cite strong evidence that use of LGG in an inpatient setting decreases length of stay. The average length of stay for AGE in our institution is 38 hours. Based on this short time frame and our small sample size, we were unable to demonstrate any benefit of LGG therapy on this outcome (data not shown). However, starting LGG on admission could have an effect after discharge by hastening the child’s return to school and parents’ return to work. Neither was measured in our study because health outcomes after discharge were beyond the scope of our rapid implementation QI project. Second, LGG is considered a dietary supplement by the Food and Drug Administration. Therefore, the dosage contained in each capsule may not be as precise as with a drug regulated by the Food and Drug Administration, and it is not covered by most prescription insurance. To overcome these potential issues, we selected a commercially available LGG formulation that best evidence suggests would yield the greatest therapeutic benefit (10115 colony-forming units).9 We also worked with our outpatient pharmacy to reduce the out-of-pocket expense to the family by offering prescriptions of remaining doses of LGG, rather than requiring purchase of a 30-pill package. This second barrier has generated interest in family preferences for LGG. Because most patients’ insurance will not cover the cost of LGG, parents are faced with a decision at discharge of whether they are willing to pay out-of-pocket to complete the 7-day course to potentially shorten the duration of diarrhea by 1 day. Viewed from this perspective, LGG is a preference-sensitive decision.26 We are currently studying parental preferences through the development and testing of a decision aid that engages families in the decision to give LGG to their child.

Finally, we have begun to spread the framework of rapid adoption of evidence-based practice using QI science. Current efforts within our institution include rapid implementation of published evidence-based guidelines for the management of first urinary tract infection,27 ongoing implementation of evidence and shared decision making for osteomyelitis,28 and planned implementation of evidence-based guidelines for the management of community-acquired pneumonia.29

CONCLUSIONS

The rapid implementation of evidence-based practice is possible when using improvement science methods. Keys to the success of our specific project were interdisciplinary collaboration, use of an EMR, and identification and mitigation of failures.

ACKNOWLEDGMENTS

We thank the CCHMC Hospital Medicine faculty and pediatric residents for their enthusiasm and commitment, as well as Evaline A. Alessandrini, Melissa Healey, Trina Hemmelgarn, Diane Herzog, Betsy List, Gayle Lykowski, Kate Rich, and Karen Tucker, whose collaborative efforts made this possible.

REFERENCES


April 15, 2011

Use of *Lactobacillus rhamnosus GG* in children with acute gastroenteritis

**Clinical Question**

- **P (population/problem)**: In children with acute gastroenteritis (AGE)
- **I (intervention)**: is the use of *Lactobacillus rhamnosus GG* in addition to oral rehydration solution (ORS)
- **C (comparison)**: compared to ORS alone
- **O (outcome)**: effective in reducing the duration of diarrhea?

**Target Population:**

**Included:** Overall healthy children aged 2 months to 18 years with acute gastroenteritis, with or without fever or vomiting (AGE defined as a decrease in the consistency of stools and/or an increase in the frequency of evacuations (≥ 3/day) lasting less than 7 days)

**Excluded:**
- children with underlying chronic diseases (mainly immuno-compromised patients, and including debilitated state or malignancies and chronic conditions that can increase intestinal mucosal permeability)
- premature infants
  
  *(Boyle 2006 [S6])*  

**Recommendation**

It is recommended to administer *Lactobacillus rhamnosus GG* (LGG) to children with acute gastroenteritis to reduce the duration of diarrhea, risk of protracted diarrhea and duration of hospitalization *(Szajewska 2007 [1a], Guarino 2008 [5a], Local Consensus [S])*.

To obtain best efficacy:
- start LGG treatment as soon as possible
- at a dose of at least 10^10 colony forming units per day (CFU/day)
- for 5 to 7 days

*(Szajewska 2007 [1a], Guarino 2008 [5a], Guarino 2008 [S])*.

**Note:** The criterion for efficacy of LGG for treatment of acute gastroenteritis is the presence of 10 billion CFU. It is important to determine that the product meets this criterion. One such product readily available locally is Culturelle capsules; Amerifit, Inc. (the product is gluten free but contains milk proteins). Culturelle for Kids contains only 1 billion CFU per dose, and other available probiotic products do not contain the LGG organism.

Available in capsules; the contents of the capsules can be dissolved in water for oral administration.

**Relevant Cincinnati Children’s Hospital Medical Center (CCHMC) policies / procedures**

CCHMC – Evidence-Based Clinical Care Guideline: Acute Gastroenteritis(2006) states that:

- It is recommended that probiotics be considered as adjunctive therapy, as they have been shown to reduce the duration of diarrhea *(Allen 2010 [1a])*.
- Family preference may be central to the decision to use probiotics.
- Parameters influencing the family’s decision may include cost, degree of potential benefit, availability and unverified effectiveness of commercial products *(CCHMC 2006 [S])*.

**Discussion/summary of evidence**

The grade of the body of evidence supporting this recommendation is high. Although the standard treatment of acute diarrhea remains to be an oral rehydration solution (ORS), probiotics have gained an important role as adjuvant
therapy. A large number of trials, including randomized controlled trials (RCTs), and several well-designed meta-analyses reported that probiotics exert clinically significant antidiarrheal effects, particularly in children.

Though LGG has primarily been studied in preschool children, it has been tested in children older than 5 years and in adults, with similar results as that for younger children (Szymanski 2006 [2a]; Khanna 2005 [2a]). The management of acute gastroenteritis is the same for older as for younger children, although the prevalence of the condition is much lower among older children. Considering the available evidence and the safety profile of probiotics, the recommendation for use of LGG as treatment for acute diarrhea can be generalized to include older children (Local Consensus [5a]).

Clinical outcomes

Four meta-analyses have been published on the effect of probiotics in the treatment of acute infectious diarrhea (Szajewska 2001 [1a]; Van Neel 2002 [1a]; Huang 2002 [1a]; Allen 2010 [1a]). In all these papers, authors compared the effect of different probiotic strains to oral rehydration in children with AGE; one of the papers included in the analysis of results some RCTs performed on both pediatric and adults (Allen 2010 [1a]).

Despite the significant heterogeneity between the studies, all meta-analyses demonstrated that probiotics, and particularly lactobacilli, reduced the duration of an acute diarrheal episode by approximately 1 day. On the other hand, beneficial effects of probiotics seem to be strain-specific and pooling data on different strains may result in misleading conclusions.

A recent meta-analysis of RCTs involving 988 children with acute infectious diarrhea found that LGG is associated with a significant reduction in diarrheal duration (7 RCTs, 876 infants; weighted mean difference (WMD) -1.1 days, 95% Confidence Interval (CI): -1.9 to -0.3), particularly of Rotavirus diarrhea (WMD -2.1 days, 95% CI: -3.6 to -0.6), risk of diarrhea longer than 7 days (1 RCT, Relative Risk (RR): 0.25, 95% CI: 0.09 to 0.75), and duration of hospitalization (3 RCTs, number of participants =535; WMD -0.58, 95% CI: -0.8 to -0.3) (Szajewska 2007 [1a]).

There is only one RCT that reports a head-to-head comparison of the efficacy of the following probiotic strains:

A- LGG
B- Saccharomyces boulardii
C- Bacillus clausii
D- a mixture including L. bulgaricus, S. thermophiles, L. acidophilus and B. bifidum
E- Enterococcus faecium SF68

The authors demonstrated that only A (LGG) and D (the mixture) were effective in reducing duration and severity of diarrhea (p<0.001) (Canani 2007 [2a]).

Dose-dependent efficacy

An early meta-analysis reported dose-related efficacy for lactobacilli preparations against gastroenteritis (Van Neel 2002 [1a]). A positive linear association between the load of the Lactobacillus dose and the reduction in diarrhea duration in days has been noted (p<0.01).

This important concept emerged again from a recent review; probiotic efficacy was correlated in a linear fashion with bacterial load; the minimal effective dose being at least 10x10⁷ CFU/day (Gandhi 2008 [5a]).

In addition, a dose-dependent effect of LGG on the rotaviral shedding has been demonstrated. In an open-label RCT aimed to assess the effectiveness of different Lactobacillus rhamnosus doses on the fecal Rotavirus concentrations in children with diarrhea, authors compared three groups of patients receiving an high-dose (6x10⁸ CFU), a low-dose (2x10⁷ CFU) or no probiotic supplementation. After 3 days of treatment only the high-dose group showed a significant (more than 80%) reduction of fecal Rotavirus concentration from the baseline concentration (p=0.012) (Fang 2009 [2b]).

In conclusion, LGG is effective in reducing duration of acute diarrhea in children, and its effect depends on the dose administered and the timing of initiation of the treatment (early treatment is better). The effect is highly significant among patients with watery diarrhea and viral gastroenteritis, but not among those with invasive bacterial diarrhea. The effect is more evident among children in developed countries compared with those in developing countries.
Health Benefits, Side Effects and Risks

Health benefits
The health benefits for LGG administration in adjunct to ORS consist of reduction of diarrhea duration, reduction in risk of having a protracted diarrhea and reduction of duration of hospitalization.

Indirectly, the use of LGG could lead to a reduction of AGE-related costs in terms of work days lost by the family and days of hospitalization; and the routine use of LGG in inpatients and community children with acute diarrhea could reduce the exposure to nosocomial and daycare infection.

Side Effects
Probiotics are generally regarded as safe, and side effects in ambulatory care have rarely been reported. Bacterial translocation, sepsis, and the risk of carrying antibiotic resistance plasmids that may spread resistance to antibiotics have been reported (Egervar 2007 [4a] Kayser 2003 [4a]). The latter has been reported for some probiotics, such as L. reuteri ATCC 55730 and Enterococcus faecium but not for LGG.

Risks
The risk for bacteremia and sepsis after LGG ingestion has been reported in some case reports involving infants and children with severe underlying diseases like short-gut syndrome, prematurity, cerebral palsy or cardiac surgical diseases; all these children required parenteral nutrition through CVC or jejunostomy feeding. (Boyle 2006 [5a]). No risks have been reported by using LGG in cohorts of children with AGE involved in clinical trials.

References/citations (evidence grade in [ ]; see Table of Evidence Levels following references)


**Guidelines that include LGG as a treatment for acute gastroenteritis in children**

A. Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for acute gastroenteritis (AGE) in children aged 2 months through 5 years. [5a] [http://www.cincinnatichildrens.org/evidence](http://www.cincinnatichildrens.org/evidence).


**Other references**

*Largest RCT on the use of LGG in children (included in cited meta-analysis)*


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Note: Full tables of evidence grading system available in separate document:

- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)
- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation (abbreviated table below)

**Table of Evidence Levels** (see note above)

<table>
<thead>
<tr>
<th>Quality level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a or 1b</td>
<td>Systematic review, meta-analysis, or meta-synthesis of multiple studies</td>
</tr>
<tr>
<td>2a or 2b</td>
<td>Best study design for domain</td>
</tr>
<tr>
<td>3a or 3b</td>
<td>Fair study design for domain</td>
</tr>
<tr>
<td>4a or 4b</td>
<td>Weak study design for domain</td>
</tr>
<tr>
<td>5</td>
<td>Other: General review, expert opinion, case report, consensus report, or guideline</td>
</tr>
</tbody>
</table>

†a = good quality study; b = lesser quality study

**Table of Recommendation Strength** (see note above)

<table>
<thead>
<tr>
<th>Strength</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Strongly recommended”</td>
<td>There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).</td>
</tr>
<tr>
<td>“Recommended”</td>
<td>There is consensus that benefits are closely balanced with risks and burdens.</td>
</tr>
<tr>
<td>No recommendation made</td>
<td>There is lack of consensus to direct development of a recommendation.</td>
</tr>
</tbody>
</table>

**Dimensions:** In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (direct benefit)
4. Burden to patient of adherence to recommendation (cost, hassle, discomfort, pain, motivation, ability to adhere, time)
5. Cost-effectiveness to healthcare system (balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)
6. Directness (the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])
7. Impact on morbidity/mortality or quality of life

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Supporting information

Introductory/background information

Acute gastroenteritis is an extremely common problem in childhood, particularly in the first three years of life. In developed countries it is usually a mild disease, however, AGE is associated with a substantial number of hospitalizations and high costs. Dehydration is the main clinical feature and generally reflects disease severity. Rehydration is the key treatment and drugs are generally not necessary, but could help to reduce duration of diarrhea, number of evacuations and, consequently dehydration and severity of the disease (Guzzino [5a]).

A number of drugs have been proposed as an adjunct to rehydration. A number of probiotic strains have been tested to date, but proof of efficacy is compelling only for a few. The rationale for the use of probiotics to treat and prevent diarrheal diseases is based on the assumption that they modify the composition of the colonic microflora and act against enteric pathogens (Guzzino [5a]).

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Search strategy

1) **Databases:** MEDLINE, Cochrane Database of Systematic Reviews
   **Search Terms:** gastroenteritis/tw, gastroenteritis/MeSH acute diarrhea/MeSH, acute diarrhea/tw probiotic/tw, probiotics/MeSH Lactobacillus/tw, Lactobacillus/MeSH child*
   **Filters:** Publication date: 1980 to present Humans English language “all child (0 to 18 years)”
2) Additional articles identified by the author and ad hoc reviewers
3) Additional articles identified from reference lists of reviewed articles

Applicability issues

The recommendations suggested in this BESt have a good applicability in daily clinical practice due to:
- similarity between the population included in the studies and the target population of this BESt
- feasibility of the treatment in the CCHMC clinical setting
- likelihood for a positive cost-benefit ratio for probiotic use in AGE when including hospitalization and emergency department (ED) readmission rates.

**Process measures** may include the percentage of hospitalized children with AGE who were administered *Lactobacillus rhamnosus GG* (LGG).

**Outcome measures** may include inpatient length of stay and the number of readmissions to the ED for AGE.
At CCHMC we will use a rapid Quality Improvement strategy aimed to increase the rate of administration of LGG in hospitalized preschool children with AGE, with the final objective to reduce the duration of hospitalization and the rate of readmission to the ED in children with AGE by reducing the duration of diarrhea.

The primary intervention will be education of medical and non-medical personnel working in selected units and involved in the management of children with AGE (attending physicians, fellows, residents, nurses, and pharmacists, families).

The intervention will be focused on the following points:
- education of physicians and nurses to improve the knowledge of evidence for probiotic use in AGE
- interaction with the pharmacy service to ensure availability of LGG in the appropriate formulation for inpatients
- standardization of LGG administration (time, dose, frequency and duration of the therapy)
- education of the family to ensure correct home therapy.

As the baseline value we will use the percentage of children, aged 2 months to 5 years, receiving LGG for treatment of AGE in the previous 13 months, in the same inpatient units as are used for the intervention. We will assess, with a weekly measurement during the next 6 months, the variation of the percentage of preschool children receiving LGG during hospitalization.

Copies of this Best Evidence Statement (BEST) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: [http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/definit.htm](http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/definit.htm)

Examples of approved uses of the BEST include the following:
- copies may be provided to anyone involved in the organization’s process for developing and implementing evidence-based care;
- hyperlinks to the CCHMC website may be placed on the organization’s website;
- the BEST may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents, and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any BEST adopted, adapted, implemented or hyperlinked by the organization is appreciated.

For more information about CCHMC Best Evidence Statements and the development process, contact the Anderson Center at: 513-636-2501 or HPCEInfo@cchmc.org

Note
This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed by two independent reviewers against established criteria.
CHAPTER 6
E-LEARNING AS A TOOL FOR IMPLEMENTATION
OF CLINICAL PRACTICE GUIDELINES ON ACUTE GASTROENTERITIS

6.1 Rationale of the initiative

E-learning is being explored as a tool for education in medical science with promising results. E-learning was effective in improving pediatric prescribing skills of junior doctors, and outcomes were maintained over a 3-month period [1]. Residents, registrars and nurses taking an e-learning program on pediatric cardiopulmonary resuscitation achieved a significant improvement in basic and advanced life support techniques [2]. However, the potential use of technology in medical education and transfer of knowledge to practice is not fully exploited and the impact on patient outcomes following e-learning courses has yet to be determined [3].

AGE is an ideal candidate condition for CPG implementation through e-learning, due to its huge burden and broad interest as well as a recognized target for implementation. Recently, the Federation of the Societies of Pediatric Gastroenterology Hepatology and Nutrition (FISPGHAN) indicated that e-learning programs are an educational priority and should be exploited to decrease AGE-related mortality worldwide[4].

We aimed at assessing the impact of an e-learning course on the management of AGE in children of Europe based on the CPG jointly produced by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/European Society for Pediatric Infectious Diseases (ESPID) [5] on knowledge and clinical practice in European pediatricians and general practitioners.

An e-learning approach, for the dissemination and implementation of CPGs has been designed, to be tailored to learner-specific needs and a specific project was awarded a grant by UEG within the monothematic initiatives. The e-learning event, which is the first of a series of ESPGHAN e-learning initiatives, includes a 2 hour interactive course on the management of gastroenteritis in children of Europe based on guidelines.

The TEEN-AGE project
The e-learning course is part of a more structured project, the TEEN-AGE (Tutorial European Electronic Network on Acute Gastroenteritis) project coordinated by Prof Alfredo Guarino, on behalf of ESPGHAN.

The aims of TEEN-AGE are to:

- Provide an e-learning course for dissemination and implementation of ESPGHAN/ESPID CPGs for AGE addressed to physicians from 15 European Countries
- Provide a tutorship of the learners by experts from each participating Country with the specific tasks of optimizing the course content, enrolling participants among physicians working in primary care and hospitals and following them for possible problems or questions.
- Identify local and individual factors that affect the dissemination and the applicability of the guidelines.
- Assess the impact of the e-learning course and relating it to local and individual variables by measuring two main outcomes:
  - Variation in knowledge (pre-post intervention)
  - Variation in adherence to guidelines (pre-post intervention)

Start-up with the teen-age workshop

The Workshop entitled “Online Strategies for the Implementation of European CPGs in Pediatric Gastroenterology”, held in Naples on 17-18 September 2012, was the first step of the TEEN-AGE project.

The workshop, held in Naples, Italy, was aimed at presenting the features of the TEENAGE project to representatives (Pediatric Gastroenterologists) from 11 European countries that will act as local tutors. The topics were:

- training in guidelines implementation and e-learning methodology
- contents of the e-learning intervention that will be offered in each country
- target of the intervention and modes of enrollment
- measuring the outcomes of the intervention

Target of the intervention and modes of enrollment

Participants to the workshop were introduced to the procedures of enrollment of the study population (i.e., the participants to the e-learning course). The participants (final users) enrolled in
the project are called “teenagers”, from the acronym of the project. The “teenagers” are physicians (both pediatricians and general practitioners) working with in- and out- patients who are expected to take the e-learning course and to undergo a pre- and post- course evaluation. About 30 “teenagers” will be enrolled by each tutor. Taking part to the project, “teenagers” will receive 2 EAACME credits, the certification of e-learning course attendance and a limited free access to the online version of Journal of Pediatric Gastroenterology and Nutrition.

Measuring the outcomes of the intervention

a. Knowledge outcomes

Pre- and post- e-learning course multiple-choice questionnaires have been tested by the tutors. The modifications were introduced in both the questionnaires and the course structure.

b. Clinical practice outcomes

A database for data entering clinical cases before (baseline) and after the e-learning course cases was provided to each tutor. Two slightly different databases have been realized, for inpatients and outpatients. Inpatients are defined as patients managed in a hospital, no matter if emergency room, emergency department or regularly admitted patients.

6.2 E-learning instrument and methodology

Study design

This study was a pre/post single-arm intervention study. The experimental phase was carried out from May 20th to September 30th, 2013. However, the entire project, including the e-learning course design and production, and the dataset analysis, required about 14 months (September 2012 to November 2013).

Participants

A total of 415 physicians from 11 European countries were invited to participate in the study. A tutor for each country was identified from among the members of the Scientific Committee of the Tutorial European Electronic Network on Acute Gastroenteritis (TEEN-AGE) project, in order to assist physicians in the recruitment process and resolve technical problems related to the United European Gastroenterology (UEG) website. Each tutor was asked to identify
at least 25 physicians from his/her country to be invited to participate. To obtain a randomly enrolled sample from each country and to minimize selection bias, participating physicians were identified through regional and national databases or through national scientific societies. No specific inclusion criteria were applied beyond the comprehension of English and the ability to use a computer.

*E-learning course design and production*

The e-learning course included five learning modules addressing the five key areas of AGE management based on ESPGHAN/ESPID guidelines: 1) Introduction and definitions, 2) Clinical assessment and management, 3) Oral rehydration and active treatment, 4) Other treatments, and 5) Treatment of inpatients. All of the learning materials (video, slides, evaluation questionnaires, figures, web references, checklists) were reviewed and approved by the Scientific Committee of the TEEN-AGE initiative for content and format. The course is freely available, in English, and only requires the physician to register online (http://www.e-learning.ueg.eu/courses/course-summary.html?eprs%5Br%5D=14756)20.

*Intervention*

After registering on the UEG website, each participant received a personal code to access the section containing the e-learning course and the patient data portal. All participating physicians were asked to provide their personal profile information (age, country, languages spoken, previous experience with e-learning) and other information about their practice (specialty, years of activity, inpatient/outpatient work setting). They completed a baseline and post-course questionnaire measuring their knowledge of AGE and its treatment, which included questions from a large pool of calibrated items.

At baseline, each physician also reported on his/her case management of 3 to 5 consecutive patients <5 years of age and referred for AGE, defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (>3 in 24 hours) with or without fever or vomiting. Each learner recorded clinical case information at the end of the child’s visit or, for inpatients, at the time of discharge. These cases were entered in an anonymous electronic Case Report Form (CRF). The CRF included 5 domains: child and family data, clinical features, home management, reasons for admission, and hospital management. Additionally, any
underlying chronic conditions and/or concomitant acute illnesses were recorded in the CRF to aid in the interpretation of outcomes according to case-specific risk factors. After completing the baseline phase, physicians had one month to view the five learning modules. Subsequently, they were asked to load information on another 3 to 5 consecutive cases of AGE using the same CRF. The post-course test of knowledge was the final measure.

**Definition of inappropriate interventions**

Inappropriate interventions in the management of AGE were identified by comparing the reported medical interventions, including prescriptions and procedures, with the CPG recommendations in each of the following domains: evaluation of the main signs/symptoms, concordance between the objective assessment of dehydration and the physician’s estimate, nutritional interventions, requests for blood tests, rehydration route, prescription of microbiological investigations, and prescription of probiotics, antiemetics, antibiotics, and other anti-diarrheal drugs. The same methodology for the assessment of the appropriateness of medical interventions has been used in a previous publication [6].

Inappropriate interventions were divided into major and minor violations. A major violation was defined as a) an active medical intervention not included in CPG recommendations that might negatively affect the course of the disease and/or might be associated with unnecessary costs, or b) any violation to “high grade” recommendations in the guidelines (CPG recommendations supported by level I or II evidence according to the Muir-Gray score). A minor violation was defined as a) an intervention that did not substantially change the outcome but was generally considered inappropriate, or b) any violation to “low grade” recommendations in the referral guidelines (level III, IV, and V evidence according to Muir-Gray).

To produce a quantitative estimate of adherence to the AGE CPG in this study, any major violation reduced the overall adherence by 10% and any minor violation by 5%; the final percentage score was calculated by summing the results reported for each domain, with a maximum of 100%. Scores ≥90% were considered full adherence.

Primary outcomes of the e-learning intervention were the proportion of participants whose medical interventions were fully adherent to guidelines and the scores on the knowledge questionnaires (number of correct answers out of a total of 15 questions). The amount of time taken to complete the knowledge test was also recorded in the e-learning platform as indirect proof of improved knowledge.
Ethical considerations

The study was approved by the Education Committee of ESPGHAN and conducted with the technical partnership of the UEG as part of the TEEN-AGE initiative. All participants signed written informed consent forms.

Statistical analysis

Statistical analyses were performed in the statistical computing environment R (version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria). Data for continuous variables are expressed as means ± SD. Data for categorical variables are presented as frequencies and percentages. Pre- and post-course differences in the theoretical knowledge of CPG recommendations and average adherence scores were evaluated using the Wilcoxon signed-rank test for paired samples. To examine the impact of physician- and patient-related factors on adherence, a two-level random intercept multilevel logistic regression analysis (MLRA) was used to account for the clustering of AGE cases among physicians. MLRA was conducted separately for the pre-education patient group (PreEG) and post-education patient group (PostEG) data to investigate whether factors associated with non-adherence to CPG prior to the e-learning course were consistent with inappropriate interventions after the course. Adjusted odds ratios and corresponding 95% confidence intervals were obtained using the MLR method.

All tests were two-tailed, and p values <0.05 were considered significant.

6.3 Results of the implementation of the ESPGHAN e-learning course on acute gastroenteritis

A total of 149 physicians registered for the e-learning course; ninety physicians (60%) did not complete all the modules by the established deadline. Fifty-nine (40%) of the enrolled physicians (45 females, median age 40 years, range 26–59) completed the course (Figure 1); their baseline characteristics are shown in Table 1.

Figure 6. 1. Flowchart
Participants were from Slovenia (12); Greece (11); the Netherlands (9); Portugal, Romania, and Russia (5 each); Turkey and Italy (3 each); and Poland, Belgium, and Germany (2 each). No differences in age, gender, years of practice, setting of practice, previous experience with e-learning, or previous knowledge of CPG were observed between the physicians who completed the course and those who did not.

Table 6. 1. Baseline characteristics of the enrolled physicians

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n/N (%)</th>
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<tbody>
<tr>
<td>Mean age (mean ± SD) in years</td>
<td>39.5 ± 7.57</td>
</tr>
<tr>
<td>M/F</td>
<td>14/45 (24%)</td>
</tr>
<tr>
<td>Years of practice</td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>27/59 (46%)</td>
</tr>
<tr>
<td>≥10 years</td>
<td>32/59 (54%)</td>
</tr>
</tbody>
</table>
The data of 545 children with AGE (249 females; median age 21 months, range 1–60) were registered by the participants, 281 before (PreEG, 51%) and 264 after taking the course (PostEG, 49%). Three hundred and forty-eight patients (64%) were managed in a hospital setting, and 197 (36%) were treated in an outpatient setting. A total of 25 out of 545 children (5%) presented with severe dehydration according to physician estimates. Specific clinical characteristics of the children reported on in the PreEG and PostEG assessments are shown in Table 6.2.

### Table 6.2. Characteristics of the children with AGE registered as clinical cases.

<table>
<thead>
<tr>
<th></th>
<th>PreEG</th>
<th>PostEG</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n=281</td>
<td>n=264</td>
<td></td>
</tr>
<tr>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>152/129</td>
<td>144/120</td>
<td>1</td>
</tr>
<tr>
<td>Mean age ± SD (months)</td>
<td>23.04 ± 15.46</td>
<td>23.38 ± 16.24</td>
<td>0.98</td>
</tr>
<tr>
<td>Weight-for-age (mean ± SD)</td>
<td>0.03 ± 0.9</td>
<td>0.029 ± 0.092</td>
<td>1</td>
</tr>
<tr>
<td>Inpatients</td>
<td>184/281 (65)</td>
<td>164/264 (62)</td>
<td>0.423</td>
</tr>
<tr>
<td>Outpatients</td>
<td>97/281 (35)</td>
<td>100/264 (38)</td>
<td>0.423</td>
</tr>
<tr>
<td>Chronic underlying disease</td>
<td>20/281 (7)</td>
<td>25/264 (9)</td>
<td>0.352</td>
</tr>
<tr>
<td>Concomitant acute illness</td>
<td>35/281 (12)</td>
<td>32/264 (12)</td>
<td>0.054</td>
</tr>
<tr>
<td>ORS at home</td>
<td>128/281 (46)</td>
<td>148/264 (56)</td>
<td>0.0164</td>
</tr>
<tr>
<td>Children with severe dehydration</td>
<td>13/281 (5)</td>
<td>12/264(5)</td>
<td>0.2860</td>
</tr>
</tbody>
</table>

Pre-EG = pre-education group; PostEG = post-education group; ORS = oral rehydration solution

Knowledge about the CPG on AGE treatment increased after the e-learning course, based on the scores on the 15-question knowledge test before (8.6 ± 2.7 points) and the course (12.8 ± 2.1 points, P <0.001). The response time also decreased after the course (878 ± 503 versus 579 ± 379 seconds, P <0.001) for the 59 physicians who completed the study (Figure 6.2).
Figure 6.2. Impact of e-learning on knowledge about the management of acute gastroenteritis in children before (Pre) and after the e-learning intervention (Post): A) learners’ scores, and B) time to complete the 15-question evaluation tests (as recorded by the e-learning platform).

The proportion of patients managed in full adherence with the guidelines (i.e., no inappropriate interventions or only one minor violation) increased from 33.6 ± 31.7% to 43.9 ± 36.1% (P = 0.037). Similarly, the average adherence rate increased from 87.0 ± 7.7% to 90.6 ± 7.1% (P = 0.001) (Figure 6.3).

Figure 6.3. Adherence to clinical practice guidelines for acute gastroenteritis in 545 children <5 years managed before (Pre) and after (Post) the e-learning implementation intervention: A)
average adherence percentage score, and B) proportion of patients managed in full adherence with the guidelines.

The mean proportion of patients who received inappropriate interventions in each domain was calculated. The most common violations to the CPG were orders for stool cultures in the absence of appropriate indications. Unnecessary dietary changes and inconsistent estimates of dehydration compared to objective parameters were also frequently observed. As shown in Figure 6.4, the e-learning course reduced inappropriate interventions in all of these domains. We also observed a non-significant trend toward a reduction in inappropriate nutritional interventions (P = 0.055). In all, 22% of patients were inappropriately admitted to the hospital at PreEG, compared to 15% at PostEG (P = 0.200) patients. The proportion of hospitalized children with >5% weight gain at discharge was only 25% in the PreEG and 26.5% in the PostEG (P = 0.841), which indicates that few children with at least a moderate degree of dehydration were hospitalized and that this proportion did not change after the e-learning course.

![Figure 6.4](image)

Figure 6.4. Changes in inappropriate interventions for acute gastroenteritis in children <5 years managed before (Pre) and after (Post) e-learning.
The MLRA model is shown in Table 6.3. We assessed the link between specific physician- and patient-related factors and discrepancies with the guideline recommendations. We also investigated whether these factors were still associated with inappropriate interventions after the course. Physicians who had previous knowledge of the guidelines were more likely to adhere to the CPG (OR = 0.29; 95% CI [0.10 to 0.86]; P = 0.026) before the course. However, the e-learning course bridged the gap between those who already knew the CPG and those who did not (OR = 1.92; 95% CI [0.58 to 6.37]; P = 0.289) by the end of the course. In terms of clinical characteristics, children in the PreEG with bloody diarrhea (OR = 5.75 95% CI [1.39 to 23.89]; P = 0.016) or abdominal pain (OR = 1.88; 95% CI [1.1 to 3.24]; P = 0.02) were more likely to receive inappropriate interventions at baseline (OR = 1.9; 95% CI [0.46 to 7.84], P = 0.37), but this increased risk disappeared after the course (OR = 0.61; 95% CI [0.251 to 0.49], P = 0.279). In contrast, frequent vomiting episodes (>5/day) remained associated with inappropriate management before (OR = 4.07; 95% CI [1.39 to 11.89]; P=0.01) and after the course (OR = 5.22; 95% CI [1.64 to 16.69]; P=0.005). Chronic diseases were a protective factor against non-adherence only in the PreEG group (OR = 0.24; 95% CI [0.07 to 0.86]; P=0.028).

Table 6.3. MLRA model for the estimate of the risk of imperfect adherence
<table>
<thead>
<tr>
<th></th>
<th>PreEG Odds Ratio [95% CI]</th>
<th>PreEG P</th>
<th>PostEG Odds Ratio [95% CI]</th>
<th>PostEG P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (F vs. M)</td>
<td>0.77 [0.23 to 2.59]</td>
<td>0.674</td>
<td>0.60 [0.15 to 2.41]</td>
<td>0.472</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>1.04 [0.95 to 1.15]</td>
<td>0.494</td>
<td>1.02 [0.90 to 1.14]</td>
<td>0.776</td>
</tr>
<tr>
<td>Previous experience with e-learning</td>
<td>1.26 [0.44 to 3.62]</td>
<td>0.670</td>
<td>1.67 [0.50 to 5.62]</td>
<td>0.406</td>
</tr>
<tr>
<td>Years of activity (≥10 vs. &lt;10)</td>
<td>0.62 [0.16 to 2.33]</td>
<td>0.477</td>
<td>0.21 [0.04 to 1.12]</td>
<td>0.068</td>
</tr>
<tr>
<td>Specialty (Paediatrician vs. GP)</td>
<td>1.01 [0.17 to 6.05]</td>
<td>0.992</td>
<td>1.73 [0.19 to 16.23]</td>
<td>0.630</td>
</tr>
<tr>
<td>Setting (Outpatient vs Inpatient)</td>
<td>0.56 [0.18 to 1.81]</td>
<td>0.335</td>
<td>0.31 [0.08 to 1.18]</td>
<td>0.086</td>
</tr>
<tr>
<td>Previous knowledge of CPG</td>
<td><strong>0.29 [0.10 to 0.86]</strong></td>
<td><strong>0.026</strong></td>
<td>1.92 [0.58 to 6.37]</td>
<td>0.289</td>
</tr>
<tr>
<td>Patients characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (F vs M)</td>
<td>1.10 [0.58 to 2.11]</td>
<td>0.765</td>
<td>0.88 [0.43 to 1.8]</td>
<td>0.728</td>
</tr>
<tr>
<td>Age (Months)</td>
<td>1.00 [0.97 to 1.02]</td>
<td>0.844</td>
<td>1.01 [0.98 to 1.03]</td>
<td>0.660</td>
</tr>
<tr>
<td>Chronic disease (Yes vs. No)</td>
<td><strong>0.24 [0.07 to 0.86]</strong></td>
<td><strong>0.028</strong></td>
<td>0.92 [0.22 to 3.82]</td>
<td>0.911</td>
</tr>
<tr>
<td>Concomitant acute illness (Yes vs. No)</td>
<td>1.20 [0.43 to 3.35]</td>
<td>0.725</td>
<td>1.55 [0.48 to 5.05]</td>
<td>0.465</td>
</tr>
<tr>
<td>Episodes of vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to 5 vs. &lt;3</td>
<td>1.20 [0.52 to 2.74]</td>
<td>0.668</td>
<td>0.44 [0.17 to 1.14]</td>
<td>0.092</td>
</tr>
<tr>
<td>&gt;5 vs. &lt;3</td>
<td><strong>4.07 [1.39 to 11.89]</strong></td>
<td><strong>0.010</strong></td>
<td><strong>5.22 [1.64 to 16.69]</strong></td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Abdominal pain (Yes vs. No)</td>
<td><strong>1.88 [1.10 to 3.24]</strong></td>
<td><strong>0.022</strong></td>
<td>0.61 [0.25 to 1.49]</td>
<td>0.279</td>
</tr>
<tr>
<td>Diuresis (Decreased vs. Normal)</td>
<td>0.85 [0.37 to 1.86]</td>
<td>0.651</td>
<td>0.68 [0.27 to 1.69]</td>
<td>0.403</td>
</tr>
<tr>
<td>Duration of symptoms (Days)</td>
<td>1.13 [0.92 to 1.37]</td>
<td>0.240</td>
<td>1.14 [0.91 to 1.43]</td>
<td>0.248</td>
</tr>
<tr>
<td>Stool output</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to 5 vs. &lt;3</td>
<td>0.96 [0.37 to 2.54]</td>
<td>0.942</td>
<td>2.00 [0.71 to 5.66]</td>
<td>0.191</td>
</tr>
<tr>
<td>&gt;5 vs. &lt;3</td>
<td>1.36 [0.50 to 3.75]</td>
<td>0.548</td>
<td>0.79 [0.25 to 2.48]</td>
<td>0.688</td>
</tr>
<tr>
<td>Bloody diarrhoea (Yes vs. No)</td>
<td><strong>5.75 [1.39 to 23.89]</strong></td>
<td><strong>0.016</strong></td>
<td>1.90 [0.46 to 7.84]</td>
<td>0.377</td>
</tr>
</tbody>
</table>
6.4 Discussion

E-learning is a promising strategy to improve practice, due to its universal availability, asynchronous accessibility, interactivity, presence of implementation tools (such as checklists, web references, etc.), and the low costs for the learner [7, 8]. However, there is no proof of its efficacy in improving clinical practice. Many studies used surrogate outcomes to predict such changes, such as drug and test prescriptions [1], simulations of resuscitation procedures [2] and structured clinical examination tests [9].

We demonstrated the efficacy of an e-learning educational intervention on AGE on knowledge but also its direct impact on clinical practice. The e-learning course increased the theoretical knowledge about appropriate interventions as judged by the questionnaire. This was supported by the rates of correct answers but also the reduced time to fill it. Translated into clinical practice, better knowledge is supposed to reduce the “time to effective interventions”, an added value in the physician’s daily work.

The overall adherence to CPG also significantly improved, as judged by both average adherence and mean proportion of children managed according to recommendations. However, we not only investigated the specific gaps and the criticalities in the application of evidence-based practice in pediatric AGE, but also evaluated their determinants through a specifically developed logistic regression model and examined the role of both physicians’ and patients’ features. Logistic regression showed that the e-learning course filled the gap between physicians who had a previous knowledge of CPG and those who did not, which certainly is a major result. According to this model, the presence of abdominal pain and bloody diarrhea were major determinants of non-adherence before the e-learning intervention, but this was changed after the course, indicating that the intervention reduced mismanagement triggered by clinically alarming signs.

We investigated the possible different domains of inappropriate interventions and measured the effectiveness of the medical practice in specific areas. Notably, when comparing the PreEG and the PostEG, a decrease of the violations was observed in all the domains. The e-learning education was highly effective in reducing inappropriate requests for microbiological investigations (i.e. stool cultures), which in our observation were prescribed in about one fourth of the children, with a higher proportion in hospitalized patients. The e-learning course also reduced dietary changes,
improved the estimate of the dehydration degree, decreased the use of not recommended strains of probiotics and the inappropriate use of antiemetics and antibiotics.

However, selected clinical features, such as frequent vomiting, often induce unnecessary interventions as they are perceived as worrying, and the intervention did not change this trend. Although this was an exception with the successful impact of e-learning, mismanagement of vomiting associated with the non-recommendation of antiemetics increased in the post-course. We found that a decreased diuresis was a risk factor for violations in the estimate of dehydration, probably due to overestimation. This finding probably represents a bias, because diuresis was not included in the parameters considered by the validated scoring systems (clinical dehydration scale and Gorelick score) [10, 11] but still is an important sign of dehydration. On the contrary, trained physicians were more likely to correctly rehydrate a child in presence of reduced urine output, probably due to a better awareness of the importance of this sign.

Our study had some limitations. The country distribution of participating physicians was scattered and affected by the drop-off of the enrolled trainees. Moreover, we did not consider in- and outpatients separately, but evaluated inappropriate interventions according to the setting to increase the statistical power of the observations. In conclusion, our study provides the first demonstration that e-learning is effective not only in improving knowledge about CPG, but also in increasing the consistency of clinical interventions with those recommended. These successful results have led ESPGHAN to implement its e-learning program and to use e-learning for education and training at European level.

6.5 Spreading the e-learning initiative to developing countries: the FISPGHAN working group on acute diarrhea

The FISPGHAN Working Group on Acute Diarrhea identified in 2012 the top priorities in medical intervention, education, and research that may reduce the burden of acute diarrhea in children worldwide and published its report in JPGN [4]. The aim of this WG is to identify, design and promote practical interventions related to each of the 3 fields (medical intervention, education and research) that may help to reach the priorities indicated in the 2012 report. This WG will be active until the next World Congress and present what we will be able to achieve in the 2016 World Congress.
6.6 References


CHAPTER 7
QUALITY CARE IMPROVEMENT TO REDUCE INFECTIONS
IN CHILDREN WITH LEUKEMIA

7.1 Introduction and rationale

Infections are a major cause of morbidity and mortality in children with acute leukemia being more frequent and severe than in other at-risk populations. The threat to patient’s health and life is related either to the infection as such or to the consequence that each episode may have on the children’s’ underlying condition: interruption or delay of chemotherapy, prolonged hospitalization, risk of nosocomial infections or malnutrition (1). In turn, the risk of infection is related to patient’s age and its main diagnosis, phase and characteristics of chemotherapy, absolute neutrophil count and antibiotic prophylaxis and therapy (2, 3, 4, 5, 6).

Bloodstream infections are serious events and cause a prolongation of hospital stay, increased costs and high risk of mortality. Central line-associated blood stream infection (CLABSI) rate in at-risk children varies between 0.7 and 7.4 episodes per 1000 central-line days, according to different studies (7)(8)(9)(10). However, the risk of infection significantly changes in relation to the main diagnosis, underlying patient conditions and duration of central line (7)(8). Children with acute leukemia and children undergoing bone marrow transplantation show higher infection rates when compared to children affected by other hematologic illnesses or solid tumors (8).

In studies on central-line related complications in European children with acute leukemia, infection rates ranged from 1.4 to 5.4/1,000 catheter days according to the central line characteristics (11). Other factors that further raise the risk of CLABSI in children with leukemia include blood product transfusion, parenteral nutrition and young age.

Implementation of adequate hygiene measures, appropriate management of medical devices (central line), and prevention of exposure to infections may significantly reduce the infection rate (10)(12)(13). These procedures have been reviewed by the Healthcare Infection Control Practices Advisory Committee of the Center for Disease Control and Prevention’s (CDC/HIPAC) that updated the Guidelines for the Prevention of Intravascular Catheter- Related Infections (14).

Previous studies tested the efficacy of multifaceted interventions to reduce the occurrence of infections, and particularly CLABSI, in at risk patients such as adults and children admitted to
intensive care units (15)(16). Limited evidence supports effective approach to reduce the incidence of CLABSI in this vulnerable population (7)(8).

This quality care improvement study was aimed at reducing CLABSI rate in children with acute leukemia through a multifaceted approach based on the application of best clinical/nursing practices, central-line care bundles and direct family involvement and training. We report the results obtained in the first 3 years of activity, according to the Standards for Quality Improvement Reporting Excellence (SQUIRE) (17).

7.2 Methodology

*Study design and team building*

This project originated from the collaboration between the Pediatric Infectious Diseases Unit of the University of Naples Federico II and the Pediatric Hemato-Oncology Unit (PHO) of the Santobono-Pausilipon Children’s Hospital in Naples, Italy. A combined multidisciplinary team was created, which included pediatricians with expertise in infectious diseases and onco-hematology, a pediatrician with specific knowledge in quality-care improvement methodology and microbiologists, surgeons and nurses.

*Setting and population*

Santobono-Pausilipon Children’s Hospital is the largest pediatric medical center located in the South of Italy, with over 35000 pediatric admissions in 2013. It is a major center for children with leukemia, with about 350 children in follow-up and about 40 new diagnosis of acute leukemia per year. The average daily census is 14 patients admitted in the PHO ward and 30 patients under the day hospital unit.

This quality improvement project started in April 2011 focusing on the pediatric inpatient and the day-hospital units. Children aged 2 months to 18 years admitted to the PHO unit with acute leukemia (either lymphoblastic or myeloid) were considered for inclusion. Patients managed in the same unit for other diseases or patients undergoing Bone Marrow Transplantation (BMT) were excluded because of a different risk of infection and/or managed in a specific unit. However, all educational interventions and evidence-based procedures were disseminated to the entire health-care personnel irrespective of unit affiliation.
All patients underwent chemotherapy according to the specific diagnosis and risk level according to the protocols of the Italian Association of Pediatric Hematology and Oncology (AIEOP) (REF). All children with fever were started on empiric antibiotic association of third-generation cephalosporin and amikacin according to the AIEOP 2004 protocol (18); if fever (and/or signs of inflammation) persisted more than 3 days, a second line antibiotic therapy and/or antiviral and antymycotic agents were introduced as additional empiric treatment unless microbiological investigations or imaging did not yield a specific diagnosis. A specific antimicrobial therapy was started as soon as evidence of a specific agent and its antimicrobial-resistance profile were available.

*Intervention planning*

We designed a 3-years biphasic intervention study including a first retrospective phase (1 year) and a secondary prospective intervention phase (2 years).

*Retrospective phase*

The first observational phase was aimed at reviewing the existing procedures for prevention and management of infections, monitoring nurse procedures and specifically look at the management of central line. In this phase, we analyzed the baseline incidence of infections in the 12 months before starting the implementation program. The baseline infection rates were calculated by manual-chart reviewing of eligible patients admitted at the PHO between April 2011 and March 2012 because of fever defined by a body temperature >38.5°C in one measurement or by body temperature >38°C in two consecutive measurement within 1 hour. CLABSI rate was calculated according to the Center for Disease Control definition (19) by using a standardized case registration form. This included patient data, diagnosis and disease risk, presence, location and type of CVC, fever (and other symptoms) onset and duration, hospital stay, blood tests at symptoms onset, organisms isolated from blood cultures, treatment and clinical outcomes. Pre-intervention data were used to define the baseline and set up appropriate interventions to reach the goal.

The team members met regularly for three months to set up the study protocol, practice interventions and expected effects according to the CDC and the National Association of Children's Hospitals and Related Institutions (NACHRI) Quality Transformation Efforts (16).
Prospective intervention phase

Based on the retrospective analysis, the team developed a SMART aim that was Specific, Measureable, Actionable, Relevant, and Time-bound (20) to reduce by at least 30% the infection rate in children with leukemia. In details, the intervention phase was aimed at identifying specific key drivers and developing the interventions to reduce CLABSI in the target population.

Post intervention data were obtained through a daily scan of patients and manual chart review of eligible patients admitted in two years (March 2012 and March 2014). A research nurse trained in data collection and interpretation, reviewed the list of hospital patients each weekday. On Monday morning, the research nurse would also review patients admitted during the weekend. Once a patient had been identified, the research nurse noted whether the patient met the inclusion criteria for the QI project.

The group met regularly to discuss infection rates, systematically review new events and discuss interventions and barriers to local implementation according to the Plan-Do-Study-Act (PDSA) cycle (20).

The interventions were grouped in 5 different main domains (Table 7. 1) and all were tested in two medical units (PHO ward and day-hospital service) and adapted as needed:

1) **Hygiene measure and management of central line**
A bundle including interventions for maintenance of central venous catheters (CVC) was introduced. Maximal sterile barrier precautions were reviewed and their application was routinely checked. A dedicated nurse was responsible of daily evaluation of the catheter insertion site. Hand hygiene measures were reviewed; dispensers with alcohol-containing preparations were placed in each room at patient’s bed. In addition, parents were directly involved in hand hygiene measure control. Chlorhexidine replaced povidone-iodine for CVC placement and maintenance, based on strong evidence (21).

Disinfection products consumption was monitored monthly. The ratio between the number of alcohol-containing solutions and chlorhexidine and the at-risk patients days, was used as process measure.

2) **Health-care personnel education and training**
A research nurse (RN) was specifically dedicated to infection control and procedure and events monitoring.
A 3-day course was specifically organized for nurses focusing on the procedures for intravascular catheters insertion and maintenance and on control measures to prevent CVC-related infections. The project was also presented to members of the medical and nursing staff of other units.

3) **Family education and direct involvement**
Since children with leukemia maintain a central line for about 2 years and spend at home the majority of this time, we directly involved parents in the management of central lines. A specific educational program was provided to the parents of all children with a new diagnosis of acute leukemia to instruct them about the infection prevention measures and the care of central lines. A training course on the management of central lines was delivered by a dedicated nurse to all families. The training lasted about 2 months according to parent’s autonomy and self-confidence and included 7 to 9 practical sessions on both mannequins and children with the assistance of a dedicated nurse. A video clip illustrating the procedures for asepsis and complete medication of CVC in children was specifically produced and provided to all families taking part to the training. This educational tool gave them the opportunity to view the procedures every time they want. Subsequently, the training was extended also to all families of children already managed at PHO. In addition, parents were specifically instructed to check health care personnel compliance with standard of practice also in other settings throughout the hospital (units other than PHO, such as radiology).

4) **Feedback on Performance**
Nurse performance was continuously monitored by the RN involved in the project. Determination of CLABSI events was made by personnel independent from the clinical team. An up-to-date infection rate was displayed graphically in the medical and nursing break rooms. Single infectious events were discussed with infectious diseases specialists and root cause analysis process began as soon as blood culture yielded positive results.

5) **Interaction with the microbiology unit and the pharmacy**
A revised protocol for blood culture sampling, including 3 blood cultures (at least one from peripheral vein) in the first hour after fever onset and before starting antibiotic empiric treatment was introduced in May 2012.
In parallel to the family educational program, medical kits for central-line medication were distributed to families to care they children at home.

**Table 7. 1.** Interventions composing the bundle according to the respective key-drivers
<table>
<thead>
<tr>
<th>KEY DRIVERS</th>
<th>INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hygiene measures and management of central-line</td>
<td>- Review and application of maximal sterile barrier precautions</td>
</tr>
<tr>
<td></td>
<td>- Promotion of hand hygiene</td>
</tr>
<tr>
<td></td>
<td>- Alcohol-containing preparation dispenser at patients’ bed</td>
</tr>
<tr>
<td></td>
<td>- Use of chlorhexidine for central-line placement and management</td>
</tr>
<tr>
<td></td>
<td>- Use of recommended insertion-site dressing practices</td>
</tr>
<tr>
<td></td>
<td>- Removal of central lines when no longer needed</td>
</tr>
<tr>
<td></td>
<td>- Visual Score to assess the CVC exit site</td>
</tr>
<tr>
<td></td>
<td>- Checklist for CVC daily management</td>
</tr>
<tr>
<td></td>
<td>- Checklist to record single infectious events</td>
</tr>
<tr>
<td>Health-care personnel education and training</td>
<td>- Continuous education of health-care personnel involved in the study</td>
</tr>
<tr>
<td></td>
<td>- Training course for nurses</td>
</tr>
<tr>
<td></td>
<td>- Production of local protocol for CVC management</td>
</tr>
<tr>
<td></td>
<td>- Dissemination of the local protocol to other units having contacts with</td>
</tr>
<tr>
<td></td>
<td>CVC (eg. Radiology)</td>
</tr>
<tr>
<td></td>
<td>- Checklist for surgical CVC placement</td>
</tr>
<tr>
<td></td>
<td>- Registered nurse dedicated to infection control</td>
</tr>
<tr>
<td>Family education and direct involvement</td>
<td>- Educational program for families on the role and importance of CVC</td>
</tr>
<tr>
<td></td>
<td>- Nurse dedicated to family training</td>
</tr>
<tr>
<td></td>
<td>- Practical training for parents with simulator</td>
</tr>
<tr>
<td></td>
<td>- Educational tools (booklet and CD-rom) for parents</td>
</tr>
<tr>
<td></td>
<td>- Direct parents involvement in personnel hand-washing monitoring</td>
</tr>
<tr>
<td>Health care personnel feedback and performance</td>
<td>- Monitoring of nurses activities</td>
</tr>
<tr>
<td></td>
<td>- Monitoring of antiseptic and chlorhexidine consumption</td>
</tr>
<tr>
<td></td>
<td>- Daily measurement of feverish episodes and CLABSI and monthly reporting of</td>
</tr>
<tr>
<td></td>
<td>rates</td>
</tr>
<tr>
<td></td>
<td>- Sharing of infection monitoring results</td>
</tr>
<tr>
<td>Interaction with microbiology unit and pharmacy</td>
<td>- Optimization in blood culture sampling strategies.</td>
</tr>
<tr>
<td></td>
<td>- Replacement of povidone-iodine with chlorhexidine</td>
</tr>
<tr>
<td></td>
<td>- Medical kits for CVC medication and management</td>
</tr>
</tbody>
</table>

**Outcome measures**

CLABSI rate/1000 catheter days in children with acute leukemia were considered as primary outcome. However, also the episodes of fever/1000 at-risk patient days were calculated to study the impact of interventions on the overall incidence of infections.
Central line days and patient-day denominator data were obtained by measuring the number of children with leukemia, with or without central line, present in the unit at the same time each day, as recommended by the Center for Disease Control and Prevention recommendations (14)(19). According to CDC recommendation (19), each patient with a central line contributed only 1 central line day even if the patient had more than 1 central line.

The efficacy of family training program was specifically assessed by measuring CLABSI infection rate by dividing the study population in three subgroups according to the level of training received by the family at the date of infectious episode onset.

The duration of fever, the length of hospital stay and the need of a shift from first-line antibiotic treatment were considered as secondary outcomes.

**Statistical analysis**

The research nurse recorded data and created run charts using Microsoft Excel®. Control charts display data in a timed sequence and help detecting trends and their specific causes of variations (20)(22). Data were updated monthly to reflect the infections rates. The mean rates were calculated based on the first 12 months of observation. Chi-square test was used to compare the prevalence of infection in different groups. Continuous variables during the three years of observation were analyzed by ANOVA test. Cumulative CLABSI rate with 95%CI was calculated to compare the infection rate in subgroups of children managed by families according to the level of education.

**Human Subject Protection**

The Santobono-Pausilipon Children’s Hospital institutional review board reviewed the project and considered it to be a local quality improvement initiative rather than a research involving human subjects. Informed consent beyond the standard consent for treatment for all inpatients was not required.

**7.3 Results of the implementation program**

In three years of observation, 118 children received a diagnosis of acute leukemia at the Santobono-Pausilipon Children’s Hospital and 71 of them were admitted to the PHO unit because of fever. Of them 56 patients (78.8 %) had ALL, and 15 patients (21.2 %) had AML. Of ALL patients,
19/56 children (34%) had a diagnosis of high risk ALL and 12/56 (21.4%) presented a relapse; all these children (n=31) were grouped together and classified as high risk ALL (ALL-HR).

The median age at first fever episodes was 67 months (IQR 49-138).

In the study period, 146 infectious episodes of fever were observed and their distribution was at least in part affected by the underlying condition: 29 episodes occurred in the 25 children with ALL, 77 in the 31 children with ALL-HR and 40 episodes in the 15 children with a diagnosis of AML (p= 0.04). Fifty-five of these 146 (37.6%) episodes were classified as CLABSI: 37 (67%) in children with ALL and 18 (32%) in children with AML.

The characteristics of the study population and infectious episodes are shown in Table 7.2.

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>ALL-HR</th>
<th>AML</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. General characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children</td>
<td>25 (35)</td>
<td>31 (44)</td>
<td>15 (21)</td>
<td>71</td>
<td>NA</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14/11</td>
<td>18/13</td>
<td>5/10</td>
<td>37/34</td>
<td>0.25</td>
</tr>
<tr>
<td>Age at the first episode (months)</td>
<td>55.5(29.7)</td>
<td>91(110)</td>
<td>138(141)</td>
<td>69(98.2)</td>
<td>0.035</td>
</tr>
<tr>
<td>Central line at first episode of fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hickman-Broviac</td>
<td>19</td>
<td>24</td>
<td>15</td>
<td>58</td>
<td>0.20</td>
</tr>
<tr>
<td>Groshong</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>No central line</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>B. Episodes of fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of febrile episodes/patient*</td>
<td>1.12±0.32</td>
<td>2.48±1.83</td>
<td>2.67±1.4</td>
<td>2.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>Children presenting only 1 episode (%)</td>
<td>22 (58)</td>
<td>12 (31.5)</td>
<td>4 (10.5)</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Children presenting 2 episodes (%)</td>
<td>3 (20)</td>
<td>10 (66.6)</td>
<td>2 (13.3)</td>
<td>15</td>
<td>0.0001</td>
</tr>
<tr>
<td>Children presenting ≥3 episodes (%)</td>
<td>0 (0)</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>Episodes of CLABSI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of CLABSI/patient*</td>
<td>0.38±0.49</td>
<td>0.88±1.00</td>
<td>1.13±0.99</td>
<td>0.76±0.92</td>
<td>0.02</td>
</tr>
<tr>
<td>Children with no CLABSI (%)</td>
<td>16 (45.7)</td>
<td>14 (40)</td>
<td>5 (14.3)</td>
<td>35</td>
<td>0.02</td>
</tr>
<tr>
<td>Children presenting only 1 CLABSI (%)</td>
<td>9 (37.5)</td>
<td>11 (45.8)</td>
<td>4 (16.6)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Children presenting ≥ 2 CLABSI (%)</td>
<td>0 (0)</td>
<td>6 (50)</td>
<td>6 (50)</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
§ Age reported as median and interquartile range (IQR), * Number of infectious episodes reported as mean±SD, CLABS: Central-line associated blood stream infection

The mean number of episodes per patient was higher in children with ALL-HR and AML than in children with ALL (p=0.0001, Table 2). Also the risk of presenting 2 or more episodes of fever in the study period was higher in ALL-HR and AML groups if compared with standard risk ALL (p=0.0001, Table 7.2).

The mean duration of fever and hospitalization was 4.89±2.6 and 17.64±11.9 days, respectively, with no significant variations between the three groups of diagnosis and the year of observation (Table 7.3).

Table 7.3. Secondary outcome measures and process measures during the study period

<table>
<thead>
<tr>
<th>Outcome and process measures</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children undergoing a change from first-line antibiotic therapy (n, %)</td>
<td>28/54 (51.9)</td>
<td>10/49 (20)</td>
<td>8/43 (18.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of hospitalization (mean±SD)</td>
<td>19.35±12.2</td>
<td>17.36±10.9</td>
<td>19.9±12.4</td>
<td>0.54</td>
</tr>
<tr>
<td>Duration of fever (mean±SD)</td>
<td>4.1±3.1</td>
<td>4.48±2.6</td>
<td>5.4±7.3</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean number of chlorhexidine bottles/month</td>
<td>13.14±7.27</td>
<td>32.13±5.22</td>
<td>34.50±1.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean number of alcohol-containing preparations</td>
<td>14.43±4.50</td>
<td>17.88±2.23</td>
<td>16.75±1.75</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Overall infection rates

Based on the rates observed in the baseline, the team developed a SMART aim to reduce by at least 30% the infection rate in children with leukemia. More specifically, the SMART aim was to decrease the rate of episodes of fever from 24/1000 patient at-risk days to less than 15 and the rate of CLABSI from 10/1000 CVC days to 6 within 1 year after intervention. A progressive significant reduction in the rate of fever episodes was obtained during the three years of observation (Figure 7.1).
The retrospective analysis showed a rate of 24.1/1000 at-risk patient days (95% CI 16.3 to 28.0), which decreased to 17/1000 (95% CI 13.9 to 24.2, p=0.07) in the first year and then to 14.5/1000 (95% CI 10.5 to 19.1, p=0.01) in the second year of intervention.

Figure 7.1. Overall infection rate (grey) and CLABSI rate (black) over the 3 years of observation.

An overall reduction by 41% in the rate of fever episodes was observed at the end of observation. Forty-six episodes of fever out of the 146 recorded (31.5%) needed an antimicrobial therapy shift from the first line treatment. This event was differently distributed in the three years of observation being more common in the baseline phase (51.9%) than in the first (20%) and second year (18.6%) after intervention (p=0.0001) (Table 7.3).

**CLABSI rate and etiology**

CLABSI were more common in children with ALL-HR and AML (p=0.02, Table 7.2) than in those with ALL. None of the children affected by standard risk ALL presented recurrence of CLABSI.

The occurrence of CLABSI was closely related with the duration of central-line, being significantly higher in children with prolonged dwell time (p=0.001); however no relation was found with CVC type and place of insertion. Surprisingly the risk of CLABSI was not related to the duration of neutropenia in our population.

A rate of 10.2 CLABSI for 1000 central-line days was recorded in the baseline analysis. Following the implementation phase, the CLABSI rate significantly decreased to 6.6/1000 central-line days
after the first 8 months of interventions, with a 35.3% rate reduction attributable to intervention alone. A further reduction of 42.5% was recorded in the second year of intervention reaching a final CLABSI rate of 3.8/1000 central-line days. Figure 7.2 displays the control chart with CLABSI monthly rates and the time of introduction of single interventions.

Figure 7.2. Run Chart
CLABSI rate per 1000 central-line days in children with leukemia
Coagulase negative Staphylococci were the most frequent pathogens isolated in our population. Escherichia coli was the most frequently Gram negative identified. One child had a *Staphylococcus haemoliticus* bacteremia before placing the central-line. Other microbial isolates are reported in Table 7.4.

Table 7.4. Blood culture isolates

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>Number of blood culture isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive blood culture in patients with central-line</td>
<td>54</td>
</tr>
<tr>
<td>Positive blood culture in patients without central-line</td>
<td>1</td>
</tr>
<tr>
<td>Polimicrobial infections</td>
<td>6</td>
</tr>
<tr>
<td><strong>GRAM POSITIVE BACTERIA</strong></td>
<td><strong>35</strong></td>
</tr>
<tr>
<td><em>Coagulase negative Staphylococci</em></td>
<td>25</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>11</td>
</tr>
<tr>
<td>Staphylococcus haemoliticus</td>
<td>5</td>
</tr>
<tr>
<td>Staphylococcus hominis</td>
<td>7</td>
</tr>
<tr>
<td>Staphylococcus capitis</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus warneri</td>
<td>2</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>3</td>
</tr>
<tr>
<td>Other <em>Streptococcus</em> viridans</td>
<td>1</td>
</tr>
<tr>
<td><strong>Micrococcus species</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td>Micrococcus luteus</td>
<td>2</td>
</tr>
<tr>
<td>Other <em>Micrococcus</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>1</td>
</tr>
<tr>
<td>Other non-specified Gram positive Bacilli</td>
<td>1</td>
</tr>
<tr>
<td><strong>GRAM NEGATIVE BACTERIA</strong></td>
<td><strong>25</strong></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>13</td>
</tr>
<tr>
<td><em>Pseudomonasaeruginosa</em></td>
<td>8</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>3</td>
</tr>
<tr>
<td><strong>MYCETES</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Aspergillus flavus</em></td>
<td>1</td>
</tr>
</tbody>
</table>
**Effects of family educational intervention on infection rates**

Forty-three families of children with acute leukemia were specifically trained in 18 months. None refused to take part to the educational program, but 5 families who withdrew during the study period because of anxiety, fear of causing pain to their children and “feeling of incompetence”.

The risk of CLABSI was significantly linked to the level of family training. Children managed by parents who completed the training showed a lower cumulative rate of CLABSI (2.71/1000) than those who were not trained (14.27/1000, p<0.05). Those who were in the process of training at the moment of infectious episode registration had an intermediate infection rate (4.57/1000).

**Figure 3** reports the number of events, the cumulative infection rates and the relative 95% confidence intervals.

**Figure 7. 3. Infection rates according to the level of family education**

<table>
<thead>
<tr>
<th>Level of education</th>
<th>Number of CLABSI</th>
<th>Central-line days</th>
<th>CLABSI rate/1000 central-line days</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully trained</td>
<td>3</td>
<td>1381</td>
<td>2.17</td>
<td>0.69 to 6.72</td>
</tr>
<tr>
<td>In training</td>
<td>9</td>
<td>1971</td>
<td>4.57</td>
<td>2.37 to 8.78</td>
</tr>
<tr>
<td>Not trained</td>
<td>10</td>
<td>701</td>
<td>14.27</td>
<td>7.57 to 25.52</td>
</tr>
</tbody>
</table>
Monitoring of process measures

Process measures were used to monitor monthly activity to indirectly evaluate the effects of interventions (Table 3). Chlorhexidine consumption progressively increased from 9 bottles/month in the first month to more than 30 (p<0.0001), reaching a plateau of 32-34 bottle/month. When related to the days of hospitalized patient the ratio increased from 3.4 bottles/100 days at-risk children at the beginning of intervention to 16.7 at the end of the study. Alcohol-containing preparations also significantly increased during the study period (p=0.03), reaching a plateau of about 17 bottles/month.

The compliance of health-care personnel to hand hygiene measures was estimated by an independent observer through random site observation. Compliance of healthcare workers increased from less than 50% in the first year of observation to 95%.

The use of specific checklists for the management of central-line progressively increased from 20% in the first month after introduction to 80% at the end of the project. Checklists for surgeon were poorly applied and ultimately were used by 60% of surgeons.

The number of central-line site medications daily performed in DH unit decreased from about 30/day during the observational phase to about 5-6 in the third year, as routine catheter cleansing and maintenance was entirely transferred to parents in 88% of children.

7.4 Discussion

Infections, mainly CLABSI, are a major cause of morbidity and mortality in children with acute leukemia. We demonstrated that the implementation of evidence-based bundle of interventions into daily clinical practice reduces the overall risk of infections by about 30% and the risk of CLABSI by more than 60% in this at-risk population.

We found that a specific family training provided by expert personnel and focusing on infection control and management of central lines, significantly reduced the risk of infections in children carrying catheters with prolonged dwell times.

Similar quality care improvement approaches, focused on the optimization of central-line management procedures but targeting nurses and physicians, have significantly reduced nosocomial CLABSI and improved patient safety in both adult and pediatric ICU settings (15, 23). Central-line maintenance bundles often include a program of education, retraining and monitoring
of health-care workers managing at-risk patients. However, differently from adults and neonate in ICU, children with leukemia usually live for at least 2 years with a central-line and spend a huge amount of time at home or in outpatients settings. Therefore, caregivers should be actively involved in prevention and care and this was the approach in our study. Irrespective of other interventions that were applied to all enrolled patients, training of caregivers dramatically reduced the CLABSI rate by more than 80% (fully trained vs not trained). The comparative evaluation of CLABSI rates in fully trained, in training and not trained caregivers showed clear differences in the 3 populations. In addition to the family reliability, the observed reduction of infection might be related also to the significant reduction of CVC medications performed in DH setting (up to 80%), the number of operators having contact with the patient and the reduced number of accesses in hospital setting.

Similar to previous results, there was no association between catheter features (type, number of lumens, and material) and the risk of developing CLABSI (8).

Over the 2-year post-implementation period, CLABSI incidence was significantly reduced by eliminating defects in routine practices through quality improvement methods. This included multidisciplinary team-based problem solving, iterative root cause analysis, and ongoing Plan-Do-Study-Act cycles. As recently reported by Rinke et al. (7), in our population the second year of the intervention resulted in a slightly higher decline in CLABSI rates below baseline, suggesting that a long ramp-up period may be necessary to achieve effective permanent change. The significant reduction of infections requires day-to-day adherence to evidence-based guidelines and continued re-evaluation of catheter care practices. In consistency with published data (15, 23, 24), the reduction of infections occurred without hiring additional staff or significantly increasing nursing workload, and did not need the application of novel and expensive tools or methods of care.

In addition to the reduction of CLABSI rate, other interesting results were observed during the study. An increase in infection rate was observed during the summer months (June - August) in all 3 years of study, other nurses, usually working in different units, and therefore less trained in the management of those children, are called to replace the standard nurses working at PHO. A similar, but less evident evidence, was observed in December-January, during Christmas holidays.

According to the national protocol for the management of feverish neutropenia, children who failed on first-line antibiotic therapy were started on a second-line empiric treatment with antibiotics and the adjunct of antymycotic and antiviral agents (18). During the QI initiative we
recorded a reduction in the prescription of second-line empiric treatments that reflects a substantial change in clinical practice and may result in substantial cost savings.

Our study has some limitations. One of the main barrier to local implementation of best evidence-based practice was the limited collaboration and commitment of pediatric surgeons who are usually in charge of CVC insertion. Routine use of chlorhexidine for CVC placement, routine use of surgery checklist for CVC insertion and progressive introduction of ultrasound guidance to place CVC were the intervention planned in this area. The chlorhexidine was progressively introduced in the routine practice. However, the specific checklists, although reviewed and modified in agreement with surgeons, were only partially filled in the first semester after introduction (71%), and were progressively dismissed in the second year of intervention (21% and 33% completed checklists in the past 2 semesters).

A specific training for ultrasound-assisted CVC placing was eventually provided this was not done. This technique may reduce the number of cannulation attempts and mechanical complications and is currently recommended by guidelines as the standard for long term central-line placement (19). However, other quality improvement studies reached significant results following catheter maintenance procedures rather than addressing insertion procedures that usually require specific quality improvement strategies (7).

In conclusion, a continuous education program offered to families and health-care personnel and coupled to routine application of stringent standard hygiene procedures and maintenance CVC care bundles, was effective in reducing the overall risk of infections and the risk of CLABSI in children with leukemia. The implementation of evidence-based practices and in particular training of caregivers may result in a dramatic improvement of management and eventually of survival without significant additional health-care costs or increase in nursing workload.
7.5 References


8.1 Conclusions

Clinical practice guidelines currently represent the standard of care and a support for medical practitioners in the management of acute and chronic conditions in all periods of life, from infancy to elderly. The primary aim of guidelines in pediatrics is to provide appropriate health care in specific clinical circumstances and improve the health of infants and children by ensuring that they receive up-to-date, evidence-based care.

As this thesis showed, the process that goes from the identification of a relevant clinical problem to its resolution is complex and time-consuming, and the delivery of standard care to the target population needs time and efforts.

Each one of the steps depicted in the thesis, from the development of clinical recommendations to their dissemination and local implementation, may potentially represent a barrier to local application of evidence-based recommendations.

As we showed above, the production of a high quality guideline, based on a rigorous methodology, with the participation of relevant stakeholders and target users, is the first, essential step for a correct and effective evidence-based path. However, despite the continuous production and update of referral documents, for many health conditions, there is a gap between what medical science has shown to be effective in practice and what is actually done. Although guidelines represent a major tool to improve quality of care, in most cases, the development of a guideline is not enough to change clinical practice. Further steps are always necessary and should include: pilot testing, capillary dissemination and implementation, local tailoring, and quality improvement. All these interventions need to be accurately planned, applied and monitored by expert personnel.

This thesis reported the efficacy and effectiveness of different interventions in the field of pediatric infectious diseases.

Infectious diseases are the most common illnesses in infants and children. Respiratory and gastrointestinal infections represent worldwide the major indication to medical visit, access to emergency department and hospital admission in pediatric age. In most cases, infections are
curable diseases if an appropriate management is rapidly provided. However, the high frequency and worldwide spreading result in high social and economic burden.

A routine and appropriate application of evidence-based recommendations may have a dramatic impact on the burden of all infections in pediatric age, improving child health and reducing inappropriate interventions, adverse effects and health-care expenses.

For all these reasons, and from a methodological point of view, infectious diseases represent an ideal setting to test the efficacy and applicability of guidelines.

In the field of acute intestinal infections, we observed a significant inappropriateness in current practice in Italy [1], as previously reported in other countries [2]. The gap between standard of care and local practice may be resolved by using different approaches that improve practitioners’ knowledge and significantly change their practice with consequential impact of child health. We previously demonstrated that a brief educational course (2 hours) addressed to pediatricians and based on updated guidelines for the management of acute gastroenteritis, may significantly reduce inappropriate prescriptions and improve physicians’ knowledge and clinical outcomes (duration of diarrhea) [3]. A similar approach has been proposed with the collaboration of ESPGHAN and the United European Gastroenterology by using an e-learning course directed to all European physicians managing children with acute intestinal infections. We demonstrated a good applicability of this approach and its efficacy in changing clinical practice and adherence to guidelines in 11 European countries.

E-learning is a useful tool for the dissemination of guidelines recommendations on a large scale, and this is particularly helpful for student education, rapid and continuous update of evidence and continuous medical training. However, some interventions need to be tested in a local setting, and barriers to local implementation may significantly differ between different countries, health-care settings and organizations. For all those reasons, evidence-based recommendations should be tested in daily practice by using small tests of the changes that may lead to improvement over a short period of time, barriers should be identified and a continuous monitoring should be set up. Once these small tests are refined and successfully implemented in the given context we can broaden the testing, scale up the changes and measure their effects. All this methodology is usually called “quality improvement” in health care and represents today the ideal way to put best scientific evidence in practice.
We applied a rapid cycle of improvement to increase prescription of evidence-based interventions (probiotics) in children hospitalized for acute gastroenteritis in a tertiary-care hospital [4]. In addition, we used a similar methodology to set up effective interventions to reduce infections’ rate in children with acute leukemia, and demonstrated that moving central-line management from physicians and nurse to caregivers, by using a specific training, is one of the most effective interventions to reduce the rate of blood stream infections.

Based on the data we obtained in this field, the message we can drive to health care authorities is to invest in translational medicine sciences and move part of health-care resources from production of evidence to their implementation.

The continuous investment in basic science research, a rapid translation of evidence in clinical practice and a specific training in evidence-based medicine and quality improvement, represent the future of biological sciences and medicine.
References


CHAPTER 9.
CURRICULUM VITAE

9.1 Curriculum Vitae

Main research fields:
- Quality Improvement in health care
- Systematic reviewing and evaluation of the literature
- Production of guidelines and critical evaluation of methodology for guidelines development
- Pediatric Infectious Diseases (main filed: intestinal infections, tuberculosis)
- Pediatric Gastroenterology (main filed: acute and chronic diarrhea)
- Role of probiotic strains in pediatric disease
- Vaccination in high risk children

List of publications in the years 2012 – 2015


20. Emergenza Ebola: La gestione dei bambini e neonati con potenziale infezione. Documento Congiunto elaborato da Società Italiana di Pediatria (SIP), Società Italiana di Infettivologia Pediatrica (SITIP), Società Italiana di Neonatologia (SIN), Società Italiana di Pediatria Ospedaliera (SIPO), Società Italiana di per le Malattie Respiratorie Infantili (SIMRI), Società Italiana di Emergenza Urgenza Pediatria (SIMEUP), Società Italiana di Pediatria Preventiva e Sociale (SIPPS). Novembre 2014


**Abstracts and Communications**


**9.2 Role in Scientific Societies and Working Groups**

- Member of the Council of the Italian Society of Pediatric Infectious Diseases – SITIP
- Member of the Working Group on acute diarrhea for FISPGHAN– Federation of International Societies of Pediatric Gastroenterology, Hepatology and Nutrition – FISPGHAN
- Trainee Member of the European Society of Pediatric Gastroenterology and Nutrition
- Member of Italian Society of Pediatrics – SIP
- Member of Italian Society of Pediatric Research (SIRP)

Reviewer for the following International Scientific Medical Journal:

- British Medical Journal Open
- PLOS ONE
- Journal of Pediatric Gastroenterology and Nutrition
9.3 Awards

- Research Awards for Food Safety at the Regional Congress of the Italian Society of Pediatrics 2014. “*Clostridium difficile* in pediatric age: correlation between infection and foods”
- Young Investigator Award at the Annual Meeting of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition - ESPGHAN Stockholm 2012
- Young Investigator Award at the Annual Meeting of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition - ESPGHAN Sorrento 2011
- Young Investigator Award at the Annual Meeting of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition - ESPGHAN Istanbul 2010.

9.4 Grants

- Research Grant from EcoStat Consulting UK Ltd for the collaboration to a multicenter observational study on the burden of *Clostridium difficile* infection in Italy and Spain.

9.5 Teaching Activities

- Professor at School of Nutrition of the Italian Society of Gastroenterology, Hepatology and Nutrition - SIGENP - Functional Nutrition in Pediatrics (Coordinator A. Guarino) with interventions in the events of Napoli Gen 2013/ Imola Feb 2013/ Verona Mar 2013/ Catania Ott 2013/ Roma Feb 2014
- Professor of the accredited Course for central-line management and risk of infections in pediatric hemato-oncology - Santobono Pausilipon Hospital - Oct 2012.