Towards universal guidelines for acute gastroenteritis: Comparison of recommendations in clinical practice guidelines

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Abstract

OBJECTIVE. Acute gastroenteritis (AGE) is a major cause of child mortality and morbidity. Adherence to recommendations in Clinical Practice Guidelines (CPGs) for AGE is low. It could be increased if a single, universal guideline were available, with recommendations for management. This study aimed at systematically reviewing CPGs on AGE to provide the basis for forthcoming universal guideline.
METHODS. CPGs were identified by searching MEDLINE, Cochrane-Library, National Guideline Clearinghouse and web sites of relevant societies/organizations producing and/or endorsing CPGs.
RESULTS. The definition of AGE slightly varies among the 16 CPGs identified. The parameters most frequently recommended to assess dehydration are skin turgor and sunken eyes (12/16,75%), general appearance (11/16, 68.7%), capillary refill time and mucous membranes (10/16,62.5%). Oral Rehydration Solution is universally recognized as first-line treatment. The majority of CPGs recommend low-osmolality (Na^+75 mmol/L, 10/16,62.5%) or hypo-osmolar (Na^+45-60 mmol/L, 11/16,68.7%) solution. In children who fail oral rehydration, nasogastric tube insertion for fluid administration is preferred to intravenous rehydration according to 6/16 CPGs (37.5%). Changes in diet and withdrawal of food are discouraged by all CPGs and early refeeding is strongly recommended in 14/16 (87.5%). Zinc is recommended as an adjunct to ORS by 9/16 CPGs, all from Low-Income Countries. Probiotics are considered by 7 CPGs, 4 from High-Income Countries. Antiemetics are not recommended in most CPGs (11/16). Routine use of antibiotics is discouraged.
CONCLUSION. The pattern of recommendations provides a starting point for creating a document on universal recommendations for the management of children with AGE on the basis of evidence.

Key words: acute diarrhea, children, guidelines

What is known about this subject?

- Acute gastroenteritis is a major cause of child mortality and morbidity worldwide.
- Clinical management is affected by high heterogeneity and low adherence to standard recommendations.
- FIPSGHAN aims to reduce the burden of acute diarrhea by identifying key interventions for the management of diarrhea in children

What are the new findings and/or what is the impact on clinical practice?

- The comparison of guidelines published worldwide showed relevant consistency.
- Despite some difference between low and high-income countries, the assessment of dehydration and indications to rehydration, diet and active treatment are similar.

- These findings provide the basis for universal recommendations for the management of children with acute gastroenteritis.

INTRODUCTION

Acute gastroenteritis (AGE) is a major cause of child mortality and morbidity globally, with 1-3 million deaths per year in infants and children under 5 years of age, especially in low-income countries (LIC) **[1-2]**. Of all child deaths from diarrhea, 78% occur in Africa and South-East Asia. The United Nations (UN) developed the Millennium Development Goal 4 (MDG 4) with the aim of reducing mortality of children below 5 years by two-thirds by 2015 but many countries, especially in south Asia and sub-Saharan Africa, are not on track to meet this target **[3]**. Therefore, the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea has recently outlined necessary actions for the elimination of preventable child deaths due to pneumonia and diarrhea by 2025 as part of the MDG5 **[4]**.

Even if in high-income countries (HIC) mortality due to AGE is a rare event, the health-care and economic burden of acute diarrhea remains high. AGE is a major cause of medical visits and hospitalization, and led to approximately 1.5 million outpatient visits and 220,000 hospital admissions per year in the United States, before the introduction of rotavirus vaccine **[5]**. In Europe, AGE is among the three most frequent causes of hospital admission, with an estimated annual incidence that ranges between 4% and 17% **[6-7]**.

Although the management of AGE is based on simple and straightforward interventions, there remains a high variability in practice with several unresolved issues that are strongly related to local traditions (i.e. nutritional interventions) and the availability of drugs. New treatments and management strategies have been proposed; these approaches remain controversial, such as the 'rapid intravenous rehydration' scheme **[8]** or specific medical therapies, including anti-emetics and antidiarrheal drugs **[9]**.

Evidence-based guidelines are the standard referral for clinical practice that can empower health care providers to employ effective management strategies and improve quality of care **[10]**. Several high quality Clinical Practice Guidelines (CPGs) for the management of AGE were published in the last years, but considerable variability in clinical practice persists **[11-15]**. Given this scenario, only a minority of health care providers fully comply with recommendations in CPGs. Low adherence to guidelines for AGE has been reported both in developed and developing countries **[12, 16-18]**.

Members of the Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) Working Group for AGE identified in 2012 priorities in medical intervention, education, and research that could reduce the burden of acute diarrhea in children worldwide **[19]**. The Working Group agreed that developing universal evidence-based guidelines for the management of AGE would be of value to health-care providers. Such guidelines should take into consideration differences in epidemiology and availability of local and regional resources. Agents of AGE (including cholera), local traditions and beliefs, and the costs involved in delivery of care all should be considered. The availability of

global guidelines supported by pediatric gastroenterology societies would fill an unmet need in improving the outcomes for children with AGE and increase the likelihood of meeting goals indicated by MDG4.

The aim of this study was to systematically review published guidelines on AGE, and compare the major recommendations for the management of AGE in children. This information will provide the basis for forthcoming universal guidelines for the management of AGE.

METHODS

Literature search

Relevant guidelines published in the last 15 years (from Jan 2000 to May 2015) were identified through MEDLINE (www.ncbi.nlm.nih.gov/pubmed), the Cochrane Library (www.cochranelibrary.com), and the National Guideline Clearinghouse (NGC)(www.guideline.gov). The following key words were used for research: gastroenteritis (MeSH or text word), or diarrhea (MeSH or text word) or diarrhea (text word), and infants or child preschool or child (MeSH) or child*, guideline (publication type or text word). We also looked at web sites of societies that produce and/or endorse CPGs, including the American Academy of Pediatrics - AAP (www.aap.org), Morbidity and Mortality Weekly Report (www.cdc.gov/mmwr), European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (www.espghan.org), North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (www.naspghan.org), Canadian Paediatric Society (www.cps.ca),Commonwealth Association of Paediatric Gastroenterology & Nutrition (http://www.capgan.org/), Latin American Society of Pediatric Gastroenterology, Hepatology and Nutrition (http://www.laspghan.org/), Asian Pan Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (http://appspghan.org/), Indian Academy of Pediatrics (www.iapindia.org). In addition, to obtain the largest possible number of documents, members of the FISPGHAN Working Group on Acute Diarrhea directly contacted (by e-mail) experts in all continents to obtain local guidelines and some members personally discussed the initiatives during an international congress as scientific meetings and workshops.

Inclusion/Exclusion Criteria

Starting from the definition of CPGs as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances" **[20]**, the Working Group selected guidelines, consensus statements or care protocols on the management of acute diarrhea in infants and children between 1 month and 18 years of age. CPGs published in one of the three most spoken languages (Chinese, Spanish and English)**[21]** were included. In cases of studies that referred to or endorsed previous publications, we evaluated the original document. Guidelines focusing on diarrhea prevention, vaccination, surgery, or other rare diseases and documents based on adult populations were excluded.

Comparisons

CPGs were categorized according to the following domains:

1. Definition of acute diarrhea
2. Assessment of dehydration
3. Nutritional interventions
4. Rehydration in outpatient and inpatient settings
5. Anti-diarrheal treatment
6. Anti-infectious therapy

The recommendations of each paper were reported in a table of evidence according to each domain. The quality of supporting evidence was also included when reported in the original document.
Since clinical recommendations may slightly vary according to the local setting and in order to better compare recommendations for children living in HIC and LIC, CPGs were classified according to the International Monetary Fund (IMF) list of countries with advanced economy (http://www.imf.org/external/pubs/ft/weo/2015/01/pdf/text.pdf).

RESULTS

Sixteen CPGs were included in this analysis **[5,9, 22-35]**: 8 were identified through MEDLINE, 4 collected from National and International Scientific Societies websites, 2 extracted from the NGC, 1 from a Research Institution, and 1 from Expert Opinion (**Figure 1**). Seven CPGs were developed in HIC, 8 in LIC, and 1 developed by the World Gastroenterology Organization **[26]** referred to children living either in HIC or LIC. The main characteristics of CPGs are summarized in the **Table 1**, with results of comparisons between CPGs reported according to each domain.

1) Definition of acute diarrhea

Acute diarrhea is defined in all included CPGs as a decrease in consistency of stools (loose or liquid) and/or an increase in frequency of evacuations (typically $\geq$3 in 24 hours). Some CPGs specifically focused on AGE, reported the presence of either fever or vomiting **[9, 22]** whereas others did not. Acute diarrhea is defined as diarrhea lasting $\leq$7 days by 4/16 CPGs, all developed in HIC **[9,22, 28, 31]**. Seven CPGs define acute diarrhea as lasting $\leq$14 days, all these documents were developed in LIC **[23-27, 30, 34]**. Five CPGs do not report a specific definition of diarrhea **[5, 29, 32-33, 35]**.

2) Assessment of dehydration

Most guidelines identified loss of body weight as the most reliable parameter to assess the presence and severity of dehydration. Several clinical signs and symptoms have been used to indirectly estimate the degree of dehydration. The most recommended parameters reported by the 16 CPGs were skin turgor and sunken eyes (12/16, 75%), general appearance (11/16, 68.7%), capillary refill time and mucous membranes (10/16, 62.5%) **(Table 2)**.

More recently, different scores or scales, combining more than one symptom or sign, have been studied and proposed for clinical practice. Four CPGs reported standardized clinical scores for use by practitioners managing children with AGE. The most commonly recommended score is the Clinical Dehydration Scale – CDS **[36]** recommended by 3/4 CPGs.

3) Rehydration

Oral Rehydration Solution (ORS) is universally recognized as first-line treatment of AGE and is recommended by all CPGs. Several ORS formulations are available world-wide: the majority of CPGs recommend low-osmolality (Na^+ concentration 75 mmol/L - 10/16, 62.5%) or hypo-osmolar (Na^+ concentration 45-60 mmol/L - 11/16, 68.7%) ORS. Only a minority of CPGs recommends the standard WHO solution containing 90 mmol/L of sodium (4/16, 25%). No significant difference was observed comparing the different ORS formulation used in HIC and LIC according to the Na+ concentration (p=0.56). However, it should be noted that 3 CPGs recommend the use of a specific ORS for malnourished children called ReSoMal (Rehydration Solution for Malnutrition) containing 45 mmol/L Na^+ and 40 mmol/L K^+.
Such variability likely reflects regional variations in etiologic agents causing enteritis **[37]**.
Micronutrients can be added to ORS to improve efficacy, and these preparations are referred to as "Super ORS". Only 2 CPGs consider the use of Super ORS **[22-23]** and conclude that they are not routinely recommended in clinical practice, except for zinc-containing solutions recommended in children living in developed areas.
In children who fail on oral rehydration, other rehydration options need to be attempted such as administering fluids either by nasogastric tube (NGT) or intravenously (IV). NGT is preferred to IV rehydration as second-line rehydration treatment by 6/16 CPGs (37.5%), while 9/16 (56.2%) recommend IV rehydration rather than NGT (**Figure 2**)**.** NGT is more commonly recommended in guidelines arising from HIC and IV rehydration in LIC.

4) Nutritional interventions

Changes in diet and milk (lactose) withdrawal are generally discouraged by all CPGs. Early refeeding is strongly recommended in 14/16 documents (87.5%). Most CPGs recommend that infants < 6 months should not interrupt breastfeeding (12/16, 75%) or introduce diluted or modified formula (9/16, 56.2%)

(Table 3). Lactose-free formula may be indicated in the in-patient setting (2/16, 12.5%) and in cases of diarrhea lasting > 7 days (1/16, 6.2%). Chinese, Peruvian and Botswanian CPGs recommend the use of lactose-free milk to shorten the duration of AGE (3/16). **Table 3** summarizes other recommendations for nutritional management recommended by CPGs produced in both HIC and LIC.

5) Active treatment of diarrhea

Many different pharmacological interventions have been proposed as an adjunct to ORS to reduce the severity of symptoms and the duration of illness. Active treatment with selected probiotics or drugs can be considered according to different CPGs **(Table 4)**.

Zinc was recommended as an adjunct to oral rehydration therapy by 9/16 CPGs, all from LIC. The other 7 CPGs developed in HIC discussed its use for the management of children with AGE, but did not recommend routine supplementation with Zn in non-deficient children.

Probiotics were considered by 7 CPGs (4 in HIC and 3 in LIC). One CPG developed in United States recommended discussing the use of selected probiotics with families **[28]**. South African CPGs did not recommend probiotics for routine practice, but considered the use of probiotics only for inpatient children developing nosocomial diarrhea **[25]**. Probiotics strains most commonly recommended are *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii*. Clinical recommendation also varies according to availability of products. More specifically, Australian CPGs recognize the efficacy of *Lactobacillus* strain GG and would recommend its use, but underline that probiotics are not available in the country **[31]**. Six other CPGs do not recommend probiotics (2 from HIC and 4 from LIC). Two guidelines do not discuss the use of probiotics for children with diarrhea.

Antimotility drugs, in particular loperamide, are explicitely discouraged by 12/16 CPGs. Canadian, Botswanian, Chinese, and Indian guidelines do not discuss their use for children with AGE.

Recommendations concerning other antidiarrheal agents are controversial. Racecadotril/acetorphan was recommended as a useful active treatment for diarrhea by 5/16 CPGs (1 HIC, 3 LIC, and the WGO). On the other hand, it was not recommended by 8/16 CPGs (4 HIC and 4 LIC) and it is not discussed by 3 CPGs **[9, 24, 33]**. Similarly, smectite was judged useful for AGE by 4/16 CPGs (1 HIC and 3 LIC), but not recommended by 7/16 CPGs (4 HIC and 3 LIC), and it was not included in the 5 other documents.

Anti-emetics were not recommended for use in most cases of AGE (11/16 CPGs). However, a few CPGs, including Chinese, Indian and Peruvian guidelines, consider their use for persistent vomiting. Recent ESPGHAN/ESPID CPGs discuss the use of selected molecules, principally ondansetron, for specific conditions, such as use in the emergency department with the aim of reducing hospital admissions.

However, warnings released by FDA and EMA on potentially severe side effects significantly limit these indications for use.

6) Anti-infectious therapy

Routine use of antibiotics is not recommended by all CPGs included in this analysis. The use of antibiotics is discussed by 9/16 CPGs (56.2%) and considered only in specific situations: young infants (especially those below 3 months of age), children with underlying chronic conditions or immunodeficiency at risk of developing severe or extra-intestinal dissemination, and children in the community to reduce the risk of spreading the infection. However the pattern of specific indications to use antibiotic therapy is wide and varies in each of the CPGs.

Table 4 summarizes major recommendations for anti-infectious treatment in the setting of pediatric AGE. Most guidelines recommend a pathogen-based approach (also in association with local epidemiological patterns of intestinal infection), other consider an empiric antibiotic treatment in children with dysentery.

DISCUSSION

The main pillars for the management of AGE (definition of the problem, assessment of the degree of dehydration, rapid rehydration through the oral route, age-appropriate diet, and possible use of selected products that could reduce the severity and duration of diarrhea) are common to all settings and may be applicable to most children living either in HIC or LIC. The approach to severely undernourished children, is not specifically addressed in this paper, and is likely to require a more specific and tailored clinical approach **[38, 39]**. Taken all these considerations into account, the FISPGHAN Working Group for AGE started by comparing currently available CPGs.

A prior paper on RCTs in acute diarrhea found 64 different definitions of the problem, based on inclusion criteria **[40]**. By contrast, we found a quite homogeneous definition of AGE. Diarrhea is usually defined as ‘‘a decrease in the consistency of stools (loose or liquid) and/or an increasein the frequency of evacuations (typically $\geq$3 in 24 hours), with or without fever or vomiting”. This quantitative definition, validated by a prospective community-based surveillance study **[41]**, has become the most widely accepted definition of AGE. However, when we looked at the definition of acute diarrhea, some differences emerged among CPGs, with most of the heterogeneity associated to the setting. CPGs produced in HIC define “acute” as diarrhea lasting 7 days or less, whereas guidelines produced in LIC, diarrhea was considered “acute” for up to 14 days duration. Although all CPGs agree on the definition of chronic diarrhea after 14 days of symptoms, the difference could be explained by the introduction of a third, intermediate condition, defined as either acute protracted or prolonged diarrhea that lasts 7 - 14 days **[42-45]**. The difference in definition

has potential importance in practical terms due to the application of a number of medical interventions in those children experiencing diarrhea that overcomes the definition of acute (more than 7 or 14 days): including changes in approach to alimentation, requests for additional diagnostic or microbiological tests, and the use of anti-diarrheal or anti-infectious drugs. The identification and use of a standardized definition of diarrhea also makes possible an adequate synthesis of trial results and the application of synthesized measures of outcomes in a meaningful way **[46]**.

The assessment of the degree of dehydration is the first step for the management of children with AGE, and all CPGs, both in HIC and LIC, identify the percentage of body weight loss as the best measure to assess the presence and severity of dehydration. However, in practice, pre-illness weight is only rarely available, and some authors have recently challenged its reliability [**47**]. Several scoring systems have been proposed to assess dehydration according to clinical signs and symptoms [**22**]. However, there is no single standard method, and the assessment of dehydration usually derives from a compromise between accuracy and reliability on the one hand, and operators in a specific clinical setting on the other. Even if there are significant differences between parameters suggested by individual CPG, the 5 most commonly recommended signs are: capillary refill time, skin turgor, sunken eyes, general appearance, and assessment of mucous membranes.. It should be noted that the last three parameters are part of the 4 item-based CDS, together with the presence of tears [**36, 48**].

Several studies have been conducted to validate the CDS for children 1 to 36 months of age with AGE in the emergency department (ED). Although most studies were produced by the same group, CDS was characterized by moderate-to-good inter-observer reliability and found to be useful in predicting the need for intravenous rehydration, weight gain, need for blood tests, need for hospitalization, and length of stay in the hospital and in the ED **[48-51]**. CDS, therefore, may be considered a reliable instrument to assess dehydration in children with AGE. However, it should be noted that capillary refill time is the single most sensitive and predictive sign to rule out severe dehydration **[22, 28]**. This easy-to-use parameter may be used to entrust the estimation to non-medical personnel and to field workers. It also should be emphasized that some parameters, such as skin turgor and sunken eyes, may be difficult to be assessed in severely malnourished subjects **[52]**. The dehydration assessment strategy needs to be a two-prong tool, to correctly identify those who are not dehydrated and those who are severely dehydrated. The first group could be easily managed at home using ORS to prevent dehydration. The severely dehydrated group needs to be eagerly treated in hospital setting. However the group in between (some level of dehydration) is the larger in clinical practice and needs to receive a period of intense and supervised oral rehydration.
ORS is globally accepted as the first-line treatment of AGE in children. All CPGs agree on this statement, but the composition and osmolality of recommended solutions significantly differs among CPGs: reduced

osmolarity and hypotonic solutions containing [Na^+] 75 mmol/L and [Na^+] 60 mmol/L, respectively, are largely recommended in HIC. In this setting, some guidelines have also introduced [Na^+] 45 - 50 mmol/L ORS that have a better palatability and increase child compliance to oral rehydration [28].
On the other hand, CPGs developed for LIC usually refer to WHO indication recommending [Na^+] 75 mmol ORS [34] for otherwise healthy children with AGE [23, 24, 26, 27, 29, 30, 32]. The so-called standard WHO ORS containing 90 mmol/L Na^+ is no longer commercially available in many HIC and is currently recommended only for children living in LIC with high purging diarrhea such as cholera. When compared to WHO standard ORS, reduced osmolarity ORS is associated with fewer unscheduled intravenous fluid infusions, reduced stool volume and less vomiting **[53]**. Therefore, the high Na^+ concentration ORS should be reserved only for specific cases of AGE (namely severe cholera diarrhea).
Children with severe acute malnutrition and diarrhea need to be rehydrated with specific ORS containing low sodium and high potassium concentration. Although the evidence in support are still weak **[54],** ReSoMal (Rehydration Solution for Malnutrition) containing [Na^+] 45 mmol/L and [K^+]40 mmol/L is currently recommended by CPGs for the management of malnourished children in LIC **[24, 25, 27, 55]**.

In children unable to receive ORS, rehydration can be pursued by either the enteral or parenteral routes. Enteral rehydration by nasogastric route appears to be as effective as IV rehydration, it is associated with significantly fewer major adverse events, and results in a shorter hospital stay compared with IV therapy **[22]**. According to this recent evidence, many CPGs considered enteral rehydration through NGT as a valid alternative to IV rehydration, although some physicians and families regard it as a more invasive and painful procedure. Surprisingly, almost all CPGs developed in LIC consider NG rehydration as a third-line option for children who failed on oral and IV rehydration and for severely dehydrated children. However, this recommendation is in contrast with evidence deriving from a recent systematic review, including 12 studies (in either HIC or LIC) on the efficacy of NG rehydration compared with IV treatment. The authors conclude that NG rehydration should be considered as second-line therapy, after oral rehydration, particularly in resource-limited settings where children frequently present with severe dehydration and intravascular access is technically challenging or impossible **[56, 57]**.

Overall, it could be useful to reconsider these recommendations, in preparation of a universal guidelines paper where NG intervention could be a preferred method over IV rehydration, either in HIC and LIC. Only a few CPGs specifically reported IV rehydration regimens with substantial agreement on the treatment of children in hypovolemic shock and relevant variability in the management of moderate-to-severe dehydration. However, the composition and route of rehydration still remains a matter of debate **[58].**

A further cornerstone in the management of AGE is nutritional intervention. We recorded homogeneity among recommendations given by CPGs both in HIC and LIC. Most documents recommend that children < 6 months should not interrupt breastfeeding and should not introduce modified formula. In addition, children should be refed early after rapid oral rehydration therapy (4-6 hours), with no prescription of restricted diets. Beverages with high sugar content should be avoided.

On the contrary, the use of lactose-free formula is still controversial Some guidelines recommend lactose withdrawal to shorten the duration of diarrhea. A recent Cochrane review evaluated the efficacy of lactose-free versus lactose-containing diets in children age <5 years of age **[59]**. The review of 33 trials, including 2,973 children included 29 studies conducted exclusively on in-patients, all from high- or middle-income countries. Compared with lactose-containing milk, milk products, or food stuffs, lactose-free products were associated with a reduction in the duration of diarrhea in hospitalized children by approximately 18 hours. Results were, however, different in outpatients setting, suggesting that there is no need to prescribe lactose-free formula in non-hospitalized children.

Even if AGE is generally a self-limiting disease not requiring specific therapies in addition to rehydration, active pharmacological treatments have been extensively evaluated with the aim of reducing either the duration or severity of symptoms. There is no agreement, with various CPGs providing different recommendations.

Zinc, that is recommended by WHO as first line treatment together with ORS is the only therapy recommended for LIC by almost all CPGs. According to a recent Cochrane metanalysis, zinc supplementation may shorten by around 10 hours the duration of diarrhea in children > 6 months with AGE and probably reduces the risk of prolonged diarrhea. Greater efficacy has been demonstrated in children with signs of moderate malnutrition (27 hours reduction of diarrhea) **[60].**
However, it has currently no indication in CPGs from HIC. This discrepancy is probably related to proven efficacy of zinc in children with severe malnutrition due to the effects that zinc deficiency have on severity and duration of diarrhea **[61-62]**. Administration of zinc in malnourished children might be seen as a nutritional intervention or a micronutrient replacement rather than as an active treatment of diarrhea.

Anti-emetics are not recommended in the majority of guidelines. Chinese, Indian and Peruvian CPGs consider their use for persistent vomiting. In several studies and in Cochrane reviews, it was found there is some evidence, *albeit* weak evidence, that anti-emetics such as ondansetron (a 5-HT3 serotonin antagonist) and the prokinetic metoclopramide (a dopamine antagonist) reduce the number of episodes of vomiting and may reduce the need for hospital admission **[63-66]**. The increase of diarrhea noted with both

ondansetron and metoclopramide and the potentially dangerous side effects of these drugs, in particular metoclopramide, limit their use in pediatric patients. In addition, it should be noted that the United States Food and Drug Administration released in the last years two warnings for both ondansetron and domperidone, reporting the risk of prolongation of the QT interval, which can lead to anabnormal and potentially fatal heart rhythms, including Torsade de Pointes **[67]**.

Active therapies include adsorbents (smectite) and antisecretory drugs (racecadotril) and selected probiotic strains. Some recent guidelines promote their use **[22]**. However, probiotic strains promoted for use in AGE are available in some countries but not in others. As an example, the probiotic *Lactobacillus rhamnosus* GG is formally recommended for use in Australian guidelines as an effective treatment as an adjunct to ORS. However, the absence of the product in the local marketplace limits its use in clinical practice. Similarly, guidelines from India that critically looked at western recommendations, consider the use of probiotics effective in developed areas but not in India because of lack of supporting evidence in developing settings.

Routine use of antibiotics for uncomplicated AGE is always discouraged, but in specific host-related and epidemiological conditions, and in children in which AGE is accompanied by signs of sepsis an empiric antibiotic treatment may well be necessary and appropriate. Although CPGs usually recommend an etiologic approach, this recommendation is hampered by the lack of indications to microbiological investigations. However, the presence of dysentery (bloody diarrhea) represents an indication to empiric antibiotic therapy in some contexts, such as where *Shigella* is common and entero-hemorrhagic *Escherichia coli* O157:H7 and other serotypes is uncommon. Broad-spectrum antibiotics also should be used in children with underlying immunodeficiency and severe malnutrition **[68-70]**. Secondary *Salmonella* bacteremia—with extraintestinal focal infections occurs more often in children with sickle cell anemia, and in neonates or young infants; therefore, antibiotic therapy is suggested in these children **[71]**.

CONCLUSIONS

According to this comparative analysis of recommendations, there are 6 major interventions for the management of children with AGE that are common to all countries: 1) definition of acute diarrhea, 2) evaluation of the degree of dehydration through standardized and validated scores, 3) early oral rehydration with ORS, 4) early refeeding with breast milk or age-appropriate diet, , 5) use of enteral rehydration in children who do not tolerate oral rehydration and 6) limiting diagnostic work up and microbiological investigations to selected cases. These indications are common to all CPGs and could represent pillars for the development of global recommendations for the management of AGE in children.

In keeping with the mission of FISPGHAN Working Group for acute diarrhea, and according to previously identified priorities, the findings presented in this paper set the basis for a document to report global recommendations for the management of children with AGE. However, the specific recommendations should be discussed involving experts, agencies and institutions worldwide. Several issues need to be resolved at a global level according to the following considerations:

1) Universal definition of gastroenteritis
2) Score symptom vs single signs to rule out severe dehydration or sepsis
3) Limit the use of lactose free formulas/diet to selected conditions
4) ORS composition and indications and rates of enteral and intravenous rehydration, including in severely malnourished children
5) Indications and settings for active antidiarrheal treatment and anti-infectious therapy.

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REFERENCES

1. Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010:1969-87.
2. United Nations. The Millenium Development Goals Report 2014. UN, New York 2014.
3. United Nations. The Millennium Development Goals Report 2011. UN, New York 2011.
4. Quazi S, Aboubaker S, MacLean R, et al. Ending preventable child deaths from pneumonia and diarrhea by 2025. Development of the integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea. Arch Dis Child, 2015; 100:s23-s28.
5. King CK, Glass R, Bresee JS, et al. Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep. 2003;52:1–16
6. Ogilvie I, Khoury H, Goetghebeur MM, et al. Burden of community-acquired and nosocomial rotavirus gastroenteritis in the pediatric population of Western Europe: a scoping review. BMC Infect Dis. 2012;12:62.
7. Wiegering V, Kaiser J, Tappe D, et al. Gastroenteritis in childhood: a retrospective study of 650 hospitalized pediatric patients. Int J Infect Dis. 2011;15:e401–e407
8. Bruzzese E, Lo Vecchio A, Guarino A. Hospital management of children with acute gastroenteritis. Curr Opin Gastroenterol. 2013 Jan;29:23-30.
9. National Collaborating Centre for Women's and Children's Health (UK). Diarrhoea and Vomiting Caused by Gastroenteritis: Diagnosis, Assessment and Management in Children Younger than 5 Years.National Institute for Health and Clinical Excellence: Guidance. London: RCOG Press; 2009 Apr.
10. Shekelle PG, Pronovost PJ, Wachter RM, et al. Advancing the science of patient safety. Ann Intern Med 2011;154:693–6
11. Lo Vecchio A, Giannattasio A, Duggan C, et al. Evaluation of the quality of guidelines for acute gastroenteritis in children with the AGREE instrument. J Pediatr Gastroenterol Nutr. 2011;52:183-9

12. Lo Vecchio A, Liguoro I, Bruzzese D, et al. and the Accreditation and Quality Improvement Working Group of Italian Society of Pediatrics. Adherence to guidelines for management of children hospitalized for acute diarrhea. Pediatr Infect Dis J. 2014;33:1103-8.
13. Powell EC, Hampers LC. Physician variation in test ordering in the management of gastroenteritis in children. Arch Pediatr Adolesc Med. 2003;157:978-83.
14. Freedman SB, Gouin S, Bhatt M, et al. Prospective assessment of practice pattern variations in the treatment of pediatric gastroenteritis. Pediatrics. 2011; 127:e287–95.
15. Tieder JS, Robertson A, Garrison MM. Pediatric hospital adherence to the standard of care for acute gastroenteritis. Pediatrics. 2009;124:e1081–7.
16. Mangione-Smith R, DeCristofaro AH, Setodji CM, et al. The quality of ambulatory care delivered to children in the United States. New Engl J Med. 2007;357:1515–23.
17. Freedman SB, Thull-Freedman JD, Rumantir M, et al. Emergency department revisits in children with gastroenteritis: a retrospective observational cohort study. J Pediatr Gastroenterol Nutr. 2013;57:612–618
18. Pathak D, Pathak A, Marrone G, et al. Adherence to treatment guidelines for acute diarrhoea in children up to 12 years in Ujjain, India--a cross-sectional prescription analysis. BMC Infect Dis. 2011;11:32.
19. Guarino A, Winter H, Sandhu B, et al. Acute gastroenteritis disease: Report of the FISPGHAN Working Group. J Pediatr Gastroenterol Nutr. 2012;55:621-6
20. Institute of Medicine FM, Lohr K, (eds): Clinical Practice Guidelines: Directions for a New Program. Washington, DC: National Academy Press; 1990.
21. Lewis MP, Ethnologue: Languages of the World, 2009, XVI edition, Dallas, SIL International
22. Guarino A, Ashkenazi S, Gendrel D, et al. 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. J Pediatr Gastroenterol Nutr. 2014;59:132-52.

23. Salazar-Lindo E, Polanco Allué I, Gutiérrez-Castrellón P; Grupo Ibero-Latinoamericano sobre el Manejo de la Diarrea Aguda (GILA).Guía de prácticaclínica ibero-latinoamericana sobre el manejo de la gastroenteritis aguda en menores de 5 años. AnPediatr (Barc). 2014;80Suppl 1:1-22.
24. Princess Marina Hospital. Department of Paediatrics Protocols - August 2012
25. Wittenberg DF. Management guidelines for acute infective diarrhoea/gastroenteritis in infants. SAMJ. 2012;102:2.
26. World Gastroenterology Organisation Global Guidelines. Acute diarrhea in adults and children: a global perspective. February 2012.
27. Ministry of Public Health and Sanitation (MOPHS). Scaling Up Strategy for Essential Treatments in Children Under Five Years in Kenya: Diarrhoea and Pneumonia. Implementation Plan for the Period 2011/12- 2015/16.www.publichealth.go.ke
28. Acute Gastroenteritis Guideline Team, Cincinnati Children's Hospital Medical Center: Evidence-based care guideline for prevention and management of acute gastroenteritis in children age 2 months to 18 years, http://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/gastroenteritis/ Guideline 5, pages 1-20, Dec 21, 2011.
29. College of Paediatrics, Academy of Medicine of Malaysia/Malaysian Paediatric Association. Guidelines on the management of acute diarrhea in children. 2011
30. Subspecialty Groups of Gastroenterology and Infectious Diseases; Society of Pediatrics; Chinese Medical Association; Editorial Board of Chinese Journal of Pediatrics. Experts consensus on the principles of diagnosis and treatment of diarrheal diseases in children. Zhonghua Er Ke Za Zhi. 2009;47:634-6.
31. Harris C, Wilkinson F, Mazza D, et al; Health for Kids Guideline Development Group. Evidence based guideline for the management of diarrhoea with or without vomiting in children. Aust Fam Physician. 2008;37: 22-9.
32. Bhatnagar S, Lodha R, Choudhury P, et al.; Indian Academy of Pediatrics. IAP Guidelines 2006 on management of acute diarrhea. Indian Pediatr. 2007;44:380-9.

33. A Leung, T Prince; Canadian Paediatric Society, Nutrition and Gastroenterology Committee. Paediatr Child Health 2006;11: 527-31
34. World Health Organization. The Treatment of diarrhoea: a manual for physicians and other senior health workers. -- 4th rev. 2005
35. K Armon, T Stephenson, R MacFaul, et al. An evidence and consensus based guideline for acute diarrhoea management. Arch Dis Child 2001;85:132–142
36. Bailey B, Gravel J, Goldman RD, et al. External validation of the clinical dehydration scale for children with acute gastroenteritis. Acad Emerg Med. 2010;17:583-8
37. Musekiwa A, Volmink J. Oral rehydration salt solution for treating cholera: ≤ 270 mOsm/L solutions vs ≥ 310 mOsm/L solutions. Cochrane Database Syst Rev. 2011;(12):CD003754.
38. Iannotti LL, Trehan I, Clitheroe KL, et al. Diagnosis and treatment of severely malnourished children with diarrhoea. J Paediatr Child Health. 2015;51(4):387-95.
39. Gaffey MF, Wazny K, Bassani DG, et al. Dietary management of childhood diarrhea in low- and middle-income countries: a systematic review. BMC Public Health. 2013;13 Suppl 3:S17
40. Johnston BC, Shamseer L, da Costa BR, et al. Measurement issues in trials of pediatric acute diarrheal diseases: a systematic review. Pediatrics 2010;126:222–31.
41. Baqui AH, Black RE, Yunus M, et al. Methodological issues in diarrhoeal diseases epidemiology: definition of diarrhoeal episodes. Int J Epidemiol 1991;20:1057–63.
42. Lee KS, Kang DS, Yu J, et al. How to do in persistent diarrhea of children?: concepts and treatments of chronic diarrhea. Pediatr Gastroenterol Hepatol Nutr. 2012;15:229-36.
43. Guarino A, Lo Vecchio A, Berni Canani R. Chronic diarrhoea in children. Best Pract Res Clin Gastroenterol. 2012;26:649-61.
44. Mathai J, Raju B, Bavdekar A; Pediatric Gastroenterology Chapter, Indian Academy of Pediatrics. Chronic and persistent diarrhea in infants and young children: status statement. Indian Pediatr. 2011;48:37-42.

45. Moore SR. Update on prolonged and persistent diarrhea in children. Curr Opin Gastroenterol. 2011;27:19-23.
46. Karas J, Ashkenazi S, Guarino A, et al; 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. 2015;100:359-63
47. Pruvost I, Dubos F, Chazard E , et al. The value of body weight measurement to assess dehydration in children. PLoS One. 2013;8:e55063
48. Friedman JN, Goldman RD, Srivastava R, et al. Development of a clinical dehydration scale for use in children between 1 and 36 months of age. J Pediatr 2004; 145: 201-7
49. Goldman RD, Friedman JN, Parkin PC. Validation of the clinical dehydration scale for children with acute gastroenteritis. Pediatrics 2008;122:545-9.
50. Gravel J, Manzano S, Guimont C, et al. Multicenter validation of the clinical dehydration scale for children. Arch Pediatr 2010;17:1645-51.
51. Kinlin LM, Freedman SB. Evaluation of a clinical dehydration scale in children requiring intravenous rehydration. Pediatrics 2012;129:e1211-9.
52. Dekate P, Jayashree M, Singhi SC. Management of acute diarrhea in emergency room. Indian J Pediatr. 2013;80:235-46.
53. Hahn S, Kim S, Garner P. Reduced osmolarity oral rehydrationsolution for treating dehydration caused by acute diarrhea inchildren. Cochrane Database Syst Rev2002;CD002847.
54. Kelsey D J Jones and James A Berkley. Severe acute malnutrition and infection. Paediatr Int Child Health. 2014;34:S1-S29.
55. World Health Organization. Management of severe acute malnutrition in infants and children. Available at the URL: http://www.who.int/elena/titles/full_recommendations/sam_management/en/index5.html
56. Rouhani S, Meloney L, Ahn R, et al. Alternative rehydration methods: a systematic review and lessons for resource-limited care. Pediatrics 2011;127:e748-57

57. Obonyo N, Maitland K. Fluid management of shock in severe malnutrition: what is the evidence for current guidelines and what lessons have been learned from clinical studies and trials in other pediatric populations? Food Nutr Bull. 2014;35(2 Suppl):S71-8
58. Morgan JA. Question 2: Should 0.9% saline be used for maintenance fluids in hospitalised children? Arch Dis Child. 2015;100:715-7.
59. Macgillivray S, Fahey T, McGuire W. Lactose avoidance for young children with acute diarrhoea. Cochrane Database Syst Rev 2013;10:CD005433
60. Lazzerini M, Ronfani L Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436.
61. Alhashimi D, Alhashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Cochrane Database Syst Rev2006;CD005506.
62. Szajewska H, Gieruszczak-Bialek D, Dylag M. Meta-analysis: ondansetron for vomiting in acute gastroenteritis in children. Aliment Pharmacol Ther 2007;25:393–400
63. DeCamp LR, Byerley JS, Doshi N, et al. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. Arch Pediatr Adolesc Med 2008;162:858-65
64. Carter B, Fedorowicz Z. Antiemetic treatment for acute gastroenteritis in children: an updated Cochrane systematic review with meta-analysis and mixed treatment comparison in a Bayesian framework. BMJ Open 2012;2
65. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Zofran (ondansetron): Drug Safety Communication - Risk of Abnormal Heart Rhythms Posted 09/15/2011; 2011.
66. Patro B, Golicki D, Szajewska H. Meta-analysis: zinc supplementation for acute gastroenteritis in children. Aliment Pharmacol Ther. 2008;28:713-23.
67. Patro B, Szymański H, Szajewska H. Oral zinc for the treatment of acute gastroenteritis in Polish children: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2010;157:984-988.
68. Bandin F, Kwon T, Linas MD, et al. Cryptosporidiosis in paediatric renal transplantation. Pediatr Nephrol 2009;24:2245–55.

69. Sugata K, Taniguchi K, Yui A, et al. Analysis of rotavirus antigenemia in hematopoietic stem cell transplant recipients. Transpl Infect Dis 2012;14:49–56.
70. Bok K, Green KY. Norovirus gastroenteritis in immunocompromised patients. N Engl J Med 2012;367:2126–32.
71. Shkalim V, Amir A, Samra Z, et al. Characteristics of non-typhi Salmonella gastroenteritis associated with bacteremia in infants and young children. Infection 2012;40:285-9.

FIGURE LEGENDS

Figure 1. Literature sources for retrievement of CPGs

HIC: High income countries

LIC: Low income countries

*1 document (WGO 2012) is referred to pediatric population either in developed and developing countries.

Figure 2. Schemes of rehydration recommended in CPGs according to settings.

ORS: Oral rehydration solution

IV: Intravenous

NGT: Naso-gastric tube

HIC: High income countries

LIC: Low income countries

* Bhatnagar et al. 2007 did not include hospital rehydration

Table 1. Guidelines included in the comparative analysis

Table 2. Clinical signs to estimate the degree of dehydration

Table 3. Nutritional interventions included in CPGs according to the setting

Table 4. Recommendations to anti-diarrheal and antibiotic treatment according to included CPGs