

REGULAR ARTICLE

An international consensus report on a new algorithm for the management of infant diarrhoea

Andrea Lo Vecchio^{1†}, Yvan Vandenplas^{2†}, Marc Benninga³, Ilse Broekaert⁴, Jackie Falconer⁵, Frederic Gottrand⁶, Carlos Lifschitz⁷, Paolo Lionetti⁸, Rok Orel⁹, Alexandra Papadopoulou¹⁰, Carmen Ribes-Koninckx¹¹, Silvia Salvatore¹², Raanan Shamir¹³, Michela Schäppi¹⁴, Annamaria Staiano¹, Hania Szajewska¹⁵, Nikhil Thapar¹⁶, Michael Wilschanski¹⁷, Alfredo Guarino (alfguari@unina.it)¹

1. Department of Translational Medical Science, Section of Paediatrics, University of Naples Federico II, Naples, Italy
2. Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium
3. Department of Paediatrics, Emma Children's Hospital/AMC, Amsterdam, the Netherlands
4. Department of Paediatrics, University Hospital Cologne, Cologne, Germany
5. Nutrition and Dietetics Department, Chelsea and Westminster NHS Healthcare Foundation, London, UK
6. Department of Paediatrics, Faculty of medicine, Jeanne de Flandre University Hospital, CHRU Lille, Lille, France
7. Department of Pediatrics, Section of Gastroenterology, Hepatology and Transplantation, Hospital Italiano, Buenos Aires, Argentina
8. Department of Neuroscience, Pharmacology and Child Health, University of Florence-Meyer children's Hospital, Florence, Italy
9. Department of Gastroenterology, Hepatology and Nutrition, University Children's Hospital Ljubljana, Ljubljana, Slovenia
10. Gastroenterology Unit, First Department of Paediatrics, University of Athens, Children's Hospital "Agia Sofia", Thivon, Greece
11. Paediatric Gastroenterology and Hepatology Unit, La Fe University Hospital, Valencia, Spain
12. Paediatric Department, University of Insubria, Varese, Italy
13. Schneider Children's Medical Centre of Israel, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
14. Paediatric Center, Clinique des Grangettes and Centre Médical Universitaire, Geneva, Switzerland
15. Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland
16. Gastroenterology Unit, Great Ormond Street Hospital and UCL Institute of Child Health, London, UK
17. Paediatric Gastroenterology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Keywords

Algorithm, Dehydration, Gastroenteritis, Infant diarrhoea, Prolonged diarrhoea

Correspondence

Prof Alfredo Guarino, Department of Translational Medical Science – Section of Paediatrics, University of Naples Federico II – Via Pansini 5, 80131 Naples – Italy.
Tel/Fax: 0039-0817464232 |
Email: alfguari@unina.it

Received

18 December 2015; revised 9 February 2016; accepted 12 April 2016.

DOI:10.1111/apa.13432

[†]ALV and YV contributed equally to this manuscript and should both be considered as first author.

ABSTRACT

Aim: Implementing international guidelines guarantees high standards of clinical care.

A group of experts developed an algorithm to drive the management of common gastrointestinal symptoms in infancy by paediatricians and general practitioners.

Methods: The algorithm started from the evidence-based recommendations of the European Society of Gastroenterology, Hepatology and Nutrition and the European Society of Pediatric Infectious Diseases and an updated review of the literature. We used the structured quantitative method of nominal group technique to reach a consensus.

Results: A practical algorithm for the management of infants with acute diarrhoea was designed based on the consensus reached for each statement. The management of an infant with acute diarrhoea should include a sequence of actions: (i) a semiquantitative estimate of infant dehydration through validated clinical scores, (ii) rehydration therapy and early refeeding with breast milk or regular formula and (iii) effective agents to reduce the severity and duration of the diarrhoea. Finally, in children with prolonged diarrhoea, the search for aetiology should include persistent infections or reinfections, cows' milk protein allergy and coeliac diseases. Lactose should always be withdrawn.

Conclusion: This algorithm provides an evidence-based sequence of interventions to optimise the management of infants with acute diarrhoea.

INTRODUCTION

Acute diarrhoea is a common gastrointestinal problem in infants and children, although its prevalence varies significantly in the first months of life. It is infrequently reported in infants below six months of age, accounting for about 4% of medical problems, but it rapidly increases after this age to

Abbreviations

AGE, Acute gastroenteritis; ESPGHAN, European society of paediatric gastroenterology, hepatology and nutrition; ESPID, European society of paediatric infectious diseases.

Key notes

- Practical evidence-based algorithms may help to implement guideline recommendations and improve the care that is delivered to children.
- We developed a practical algorithm to support paediatricians and general practitioners to manage acute diarrhoea in infants.
- The algorithm, which started from evidence-based recommendations and developed a sequence of interventions based on expert consensus, provides a practical implementation tool that may be adapted to local circumstances.

become the most common illness in children younger than three years of age, with an average of 0.5 to two episodes of acute diarrhoea per year (1,2).

Acute diarrhoea is defined as a decrease in the consistency of stools, that appear loose or liquid, or an increase in the frequency of evacuation with more than three bowel movements in 24 hours (2). In the vast majority of cases, acute infantile diarrhoea is the consequence of acute gastroenteritis (AGE), a gastrointestinal infection, and may be associated with vomiting or fever. It typically resolves within two to seven days.

Although it is a relatively mild disease in developed areas of the world, with few deaths occurring as a direct consequence of enteric infections, AGE represents a major cause of consultations in general practice and hospital admissions. In addition, it has a major impact on the quality of life of infected children and their families and a substantial effect on healthcare costs as well as on costs to the family, mainly due to working days lost.

High-quality guidelines have been produced worldwide to provide clinical recommendations and support healthcare providers in their practice and ensure standards of care for children (3).

The management of AGE is relatively simple and, in essence, is based on three key points: (i) providing fast rehydration with oral hypo-osmolar solution; (ii) ensuring early refeeding with breast milk or full strength lactose-containing formula or cows' milk; and (iii) considering the use of agents that are effective in reducing the intensity and duration of symptoms. Anti-infectious drugs may be considered in specific circumstances or in children at risk from this condition. Despite these simple and straightforward recommendations, the overall compliance to standards of care is far from optimal around the world (4–6).

However, in some cases, acute onset diarrhoea last longer than the expected three to seven days. Although chronic diarrhoea is defined as a duration of at least 14 days, prolonged diarrhoea of more than seven days is worrying for parents and requires medical attention (7). This article also discusses the approach to this condition in infants.

Our aim was to provide a practical tool to help physicians manage acute diarrhoea in infants. This work is part of a larger initiative that aims to offer paediatricians and general practitioners simple algorithms to guide their daily practice for management of the most common gastrointestinal symptoms in infancy: regurgitation, colic, constipation and cows' milk protein allergy. This article proposes a practical algorithm for the management of acute diarrhoea in infants. The algorithm recommends a sequence of action within a global, generalised approach, which may need to be adapted to local healthcare organisations and individual patient situations. These recommendations were developed by a group of experts after an updated review of the literature. In the absence of available evidence, the recommendations were based on expert opinion.

METHODS

The steering group adopted a standardised methodology used for the development of algorithms for the management of other common gastrointestinal symptoms in infancy, as part of an initiative promoted by the Gastroenterology Committee of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (8). In November 2014, the Steering Committee extensively reviewed and discussed the first draft of this article. During the second phase, the recommendations were rediscussed by a broader group of clinicians experienced in managing infants with gastrointestinal problems. Finally, the article was approved by every participant, resulting in an algorithm built on the initial evaluation of a child with or without risk factors and the subsequent course of the disease.

To reach consensus, a structured quantitative method was utilised. In brief, consensus was formally achieved through a *nominal group technique*. The group consisted of 22 active members each voting anonymously on each statement using a score. Before the actual voting took place, the statements had been reviewed in depth by each participant, until agreement was reached on the wording. A nine-point scale was used, with one for strongly disagree to nine for fully agree (9). It had been decided from beforehand that consensus had been reached if at least 17 (75%) of the 22 members who took part in the voting six, seven, eight or nine. Furthermore, it was decided that six and above meant agreement, with nine being an expression of stronger agreement than six.

This structured method had previously been used for the development of the European guidelines on constipation and for the Cows' Milk Related Symptom Score development (10,11).

RESULTS

Acute diarrhoea

Figure 1A reports the practical algorithm for the management of infants with acute diarrhoea formulated by the working group according to the consensus reached for each statement (Table 1).

Each item is rated from 0 to 2, and the total score ranges between 0–8, resulting in three categories: no dehydration (clinical dehydration score of zero), mild dehydration (clinical dehydration score of one to four) and moderate or severe dehydration (clinical dehydration score of five to eight) (12–15). The degree of dehydration can then be easily estimated (Table 2). Physicians as well as nurses and field workers may use capillary refill time as a single, reliable, easy-to-use sign to exclude severe dehydration, with normal being defined as up to two-seconds.

Stools and laboratory investigations should only be considered in the presence of selected risk factors, such as blood in the stools or recent travel to high-risk areas, as these are associated with an increased risk of bacterial or parasite-induced diarrhoea. The algorithm includes well-defined conditions that may drive subsequent decisions, for instance conditions related to the patient, such as an age of

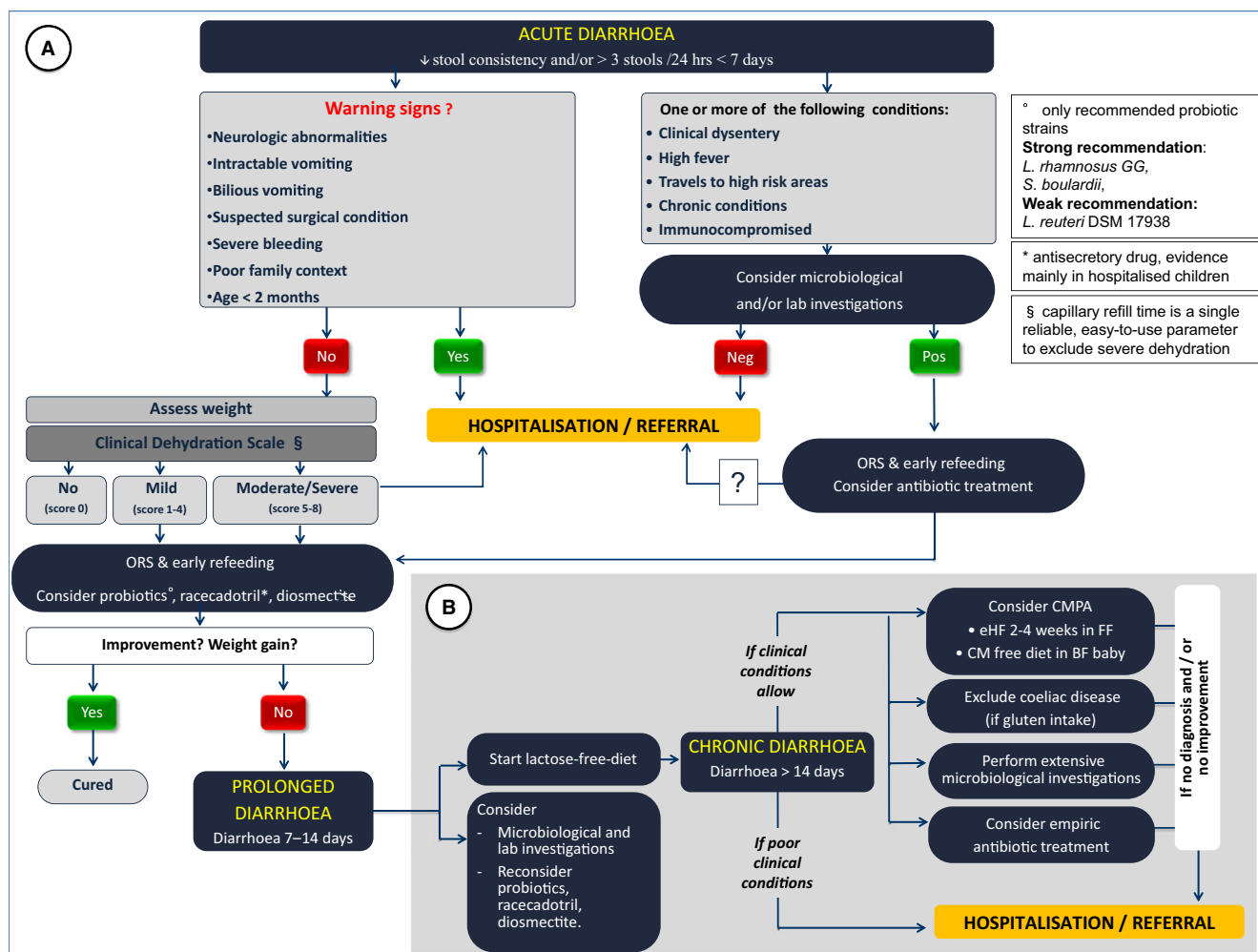


Figure 1 Algorithm for the management of acute (A) and prolonged diarrhoea (B) in infants. BF = Breastfed; CM = Cow's milk; CMPA = Cow's milk protein allergy; eHF = Extensively hydrolysed formula; FF = Formula fed; ORS = Oral rehydration solution.

less than two months or immune deficiency. Hospital admission is mandatory in cases of severe dehydration or shock, persistent or intractable vomiting that may hamper oral rehydration, bilious vomiting or other signs that may indicate a surgical condition. However, the vast majority of infants with diarrhoeal episodes can be seen in ambulatory care or managed at home.

Ambulatory treatment of infants with acute diarrhoea should always consist of oral rehydration therapy with hypo-osmolar oral rehydration solutions, to prevent or treat dehydration, followed by early realimentation (2).

During management, the repeated assessment of weight may drive further medical interventions and may provide information on the efficacy of rehydration.

The European guidelines state that breastfeeding should be continued throughout rehydration, and an age-appropriate diet should be started during or after initial rehydration of four to six hours. In any case, administering oral rehydration solution is the key treatment for AGE. It should be noted that, due to its composition, oral rehydration

solution is effective in replacing fluids and salts in infants with diarrhoea of any origin, not just infectious gastroenteritis, and should be rapidly offered to all infants. Considering the high frequency of episodes of acute diarrhoea in infants, families should be advised to have oral rehydration solution at home and offer it to their infant soon after the emission of loose, watery stools. However, it should be noted that, although oral rehydration solution is effective in preventing or treating dehydration in children with acute diarrhoea, it does not affect the duration of diarrhoea. Several agents were therefore assessed in clinical trials with regard to improving the outcome of acute diarrhoea in infants and children.

Expert opinions differ on which is the most important outcome for assessing the efficacy of therapeutic interventions. Healthcare providers consider the duration of diarrhoea as the most important outcome, while the World Health Organization (WHO) indicates that stool volume, which reflects severity, is the best parameter of recovery (16,17). Although it is not essential, active treatment for

Table 1 Statements and voting results on infant diarrhoea

Stat		Consensus	Mean
1	Acute diarrhoea is defined as a decreased stool consistency and/or increase of normal defecation frequency with more than three stools per 24 hours for less than seven days.	Yes (21/22) Agreed 95%	8.34
2	Laboratory and microbial investigations are in general not recommended in acute diarrhoea, but should be considered in cases of clinical dysentery, high fever, travels in at risk areas, associated chronic conditions and immunocompromised infants.	Yes (22/22) Agreed 100%	8.73
3	Hospitalisation is likely to be required for infants suffering from acute diarrhoea who have one of the following: neurological abnormalities, intractable vomiting, bilious vomiting, suspected surgical condition, severe bleeding and poor family context or are less than two months old.	Yes (21/22) Agreed 95%	8.60
4A	The cornerstone of acute diarrhoea treatment is oral rehydration solution (ORS) and rapid refeeding.	Yes (22/22) Agreed 100%	8.91
4B	Probiotics with evidence of efficacy – <i>S. boulardii</i> , <i>L. rhamnosus</i> GG, <i>L. reuteri</i> DSM 17938 – can be considered as an adjunct to ORS as they reduce the duration of diarrhoea by around 24 hours and as they are safe.	Yes (22/22) Agreed 100%	8.41
4C	Racecadotril can be considered as an adjunct to ORS as there is evidence that it reduces the duration of diarrhoea by around 24 hours.	Yes (20/22) Agreed 91%	7.86
4D	Diosmectite can be considered as an adjunct to ORS as there is evidence that it reduces the duration of diarrhoea by around 24 hours.	Yes (17/22) Agreed 77%	6.91
5	There is some evidence that for infants with acute diarrhoea, lactose-free feeding may reduce diarrhoea duration in hospitalised children. However, this has not been proved in the ambulatory setting.	Yes (21/22) Agreed 95%	7.17

Stat = Statement.

Diarrhoea is defined as 'loose or liquid stools and, or, an increase in the frequency of evacuations (typically three or more in 24 hours)'.

The algorithm recommends evaluating the degree of dehydration according to the clinical dehydration scale (CDS), which is supported by consistent evidence and is very easy to use by primary HCPs (2). The CDS consists of four clinical items: (i) general appearance, (ii) eyes, (iii) mucous membranes and iv) tears production (Table 2).

Table 2 Clinical dehydration scale*

Characteristics	Score		
	0	1	2
General appearance	Normal	Thirsty, restless, lethargic, but irritable when touched	Drowsy, limp, cool or sweaty; comatose or not
Eye	Normal	Slightly sunken	Very sunken
Mucous membranes	Moist	Sticky	Dry
Tears	Tears	Decreased	Absent

*Modified by Friedman et al. (12).

Score 0: No dehydration, Scores 1–4: Some dehydration, Scores 5–8: Moderate-to-severe dehydration.

diarrhoea should be considered as it may reduce the duration and severity of symptoms. The administration of specific probiotic strains for which efficacy is established, or of racecadotril or diosmectite, can be considered in addition to oral rehydration, as they all reduce the duration of diarrhoea by about 24 hours. Based on currently available data, probiotics with proven efficacy for acute diarrhoea include *Lactobacillus (L.) rhamnosus* GG and *Saccharomyces boulardii* (2,18,19). Consistent evidence is also accumulating for *L. reuteri* DSM 17938, which is included in the list of effective strains (2,18). Diosmectite and racecadotril have been reported to be effective in a broad range of conditions in both developing and developed

countries and in a broad range of ages (2). The minimal age of administration of racecadotril varies from country to country, in agreement with local regulations.

The administration of the above agents has been supported by compelling evidence of efficacy obtained in paediatric clinical trials. Based on the available evidence, all of the above agents were included in the list of effective agents for reducing duration and/or severity of acute diarrhoea in the guidelines on the management of acute gastroenteritis in children issued by ESPGHAN and the European Society for Paediatric Infectious Diseases (ESPID)(2).

According to the votes of members who took part in the development of our algorithm, there was broad consensus on the definition and treatment of diarrhoea. However, the consensus varied slightly between the experts when it came to additional therapeutic agents, with 100% voting for probiotics, 91% for racecadotril and 77% for diosmectite (Table 1).

Nutritional interventions, including modifications of feeding – such as dilution, lactose-free or cows' milk protein free formulas – and a withdrawal or elimination diet, were not recommended in otherwise healthy infants with AGE. Many different nutritional interventions, such as bananas, rice, apples and toast – the BRAT diet – and a lactose-free diet, have been proposed to limit the impact of diarrhoea in children, according to local habits and traditions. However, there has not been any convincing evidence of efficacy for any nutritional intervention in AGE (20).

An established recommendation by the WHO (21) and the recent evidence and recommendations of the ESPGHAN/ESPID guidelines (2,22) indicate that patients with diarrhoea persisting for more than seven days or those hospitalised for severe AGE may benefit from a lactose-free diet to reduce the duration of diarrhoea (Table 1).

Prolonged diarrhoea

If the diarrhoea persists beyond five to seven days, three different conditions should be taken into account: persistent infection, food intolerance or chronic gastrointestinal diseases in which diarrhoea may be the presenting symptom (Fig. 1B) (23). As the evidence supporting further diagnostic work-up and empiric interventions is very limited, primary healthcare providers may refer an infant of less than 12 months old to a specialist, depending on local health conditions. In any case, the practical approach should be based on the child's clinical condition, the weight loss, family anxiety and cooperation. Hospitalisation may be needed in those infants with poor clinical conditions and significant weight loss despite rehydration measures. In addition, they may be admitted to hospital for diagnostic purposes. If the clinical condition warrants further interventions without the need for hospitalisation and a lactose-free diet has been unsuccessful, then an extensively hydrolysed formula can be started for two weeks to exclude cows' milk protein allergy.

In parallel, laboratory investigations should be requested and include a large spectrum of enteric agents, including *Clostridium difficile* and its toxins, screening for coeliac disease with determination of specific antibodies: tissue transglutaminase immunoglobulin A and total immunoglobulin A or anti-endomysium antibodies or antideamidated gluten peptides antibodies (24). Determination of faecal elastase and a pilocarpine iontophoresis (sweat test) to rule out cystic fibrosis as a cause of malabsorption may also be considered.

In selected cases, and based on the course of the illness and its clinical features, an empiric trial with antibiotics, such as metronidazole, cotrimoxazole or nitazoxanide, may be considered to treat a potential intestinal infection or rule out small intestinal bacterial overgrowth (23).

DISCUSSION

Acute diarrhoea is a common problem in infants and children, and strong, straightforward, good-quality recommendations for its management are available (3). However, infants presenting with diarrhoea are often mismanaged and receive unnecessary investigations and medical treatments (5).

The practical algorithm proposed by this article will help general practitioners and paediatricians to diagnose and manage acute diarrhoea in infants under the age of 12 months, focusing on the degree of dehydration based on easy-to-use clinical and validated parameters, early rehydration with oral rehydration solutions, the use of

effective therapeutic interventions, such as probiotics, racecadotril and diosmectite, and limiting unnecessary investigations, dietary interventions and ineffective and not recommended drugs.

It should be noted that a specialist consultation or hospital referral should be considered in patients with underlying chronic conditions such as: very young age, rapid worsening of clinical features or difficulties in accomplishing appropriate rehydration, including refusing oral rehydration or breastfeeding and the presence of vomiting.

In addition, for children with prolonged or chronic diarrhoea, it should be always considered that diarrhoea might be the symptom of the onset of primary intestinal diseases with malabsorption (e.g. carbohydrate malabsorption or coeliac disease) or systemic disorders such as cows' milk allergy, extraintestinal infections (i.e. urinary infection, sepsis), poisoning, metabolic diseases and immunodeficiencies (22).

The diagnosis and management of some of these diseases may be challenging, as may be the case for cows' milk allergy, as it has a broad pattern of nonspecific presenting symptoms or diagnostic tests. In addition, the evidence driving the diagnostic work-up and medical interventions in infants with prolonged or chronic diarrhoea is very limited (7,21). Therefore, infants with prolonged or chronic diarrhoea who do not respond to treatment should be referred to a paediatric gastroenterologist.

CONCLUSION

The proposed algorithm was based on either the evidence or on expert consensus when the evidence was insufficient. As evidence on several aspects of these topics was quite limited, much of it is based on expert opinion.

The management of an infant with acute diarrhoea should include a sequence of actions: 1) a semiquantitative estimate of infant dehydration through validated clinical scores, 2) rehydration therapy and early refeeding with breast milk or regular formula and 3) effective agents to reduce the severity and duration of the diarrhoea. Finally, in children with prolonged diarrhoea, the search for aetiology should include persistent infections or reinfections, cows' milk protein allergy and coeliac diseases. Lactose should always be withdrawn.

This algorithm may contribute to the application of evidence-based recommendations to infants with diarrhoea in a local setting, and its validation in clinical practice may significantly improve the quality of healthcare.

ACKNOWLEDGEMENT

We are also grateful to the following for their input: Professor H Badriul (University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia), M Morais (Universidade Federal de São Paulo, Brazil), M Miqdady (Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates), S Osatakul (Prince of Songkla University,

Songkhla, Thailand) and Fügen Çullu Çokugras (İstanbul University, Cerrahpaşa Medical Faculty, İstanbul, Turkey).

CONFLICTS OF INTEREST

A number of the authors have relationships with companies relevant to the subject matter of this article. Due to space limitations, a full list appears in Data S1.

References

- Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, Di Prima L, et al. Paediatric Study Group on Gastrointestinal Symptoms in Infancy. Gastrointestinal symptoms in infancy: a population-based prospective study. *Dig Liver Dis* 2005; 37: 432–8.
- Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H., 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.
- Lo Vecchio A, Giannattasio A, Duggan C, De Masi S, Ortisi MT, Parola L, 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.
- Mangione-Smith R, DeCristofaro AH, Setodji CM, Keesey J, Klein DJ, Adams JL, et al. The quality of ambulatory care delivered to children in the United States. *N Engl J Med* 2007; 357: 1515–23.
- Lo Vecchio A, Liguoro I, Bruzzese D, Scotto R, Parola L, Gargantini G, et al. Accreditation and Quality Improvement Working Group of Italian Society of Pediatrics. Adherence to guidelines for management of children hospitalized for acute diarrhoea. *Pediatr Infect Dis J* 2014; 33: 1103–8.
- Pathak D, Pathak A, Marrone G, Diwan V, Lundborg CS. 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.
- Giannattasio A, Guarino A, Lo Vecchio A. Management of children with prolonged diarrhea. *F1000Res* 2016; 5: F1000 Faculty Rev-206.
- Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Guarino A, et al. Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. *Acta Paediatr* 2016; 105: 244–52.
- McMurray AR. Three decision-making aids: brainstorming, nominal group, and Delphi technique. *J Nurs Staff Dev* 1994; 10: 62–5.
- Vandenplas Y, Dupont C, Eigenmann P, Host A, Kuitunen M, Ribes-Koninckx C, et al. A workshop report on the development of the Cow's Milk-related Symptom Score awareness tool for young children. *Acta Paediatr* 2015; 104: 334–9.
- Tabbers MM, Di Lorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014; 58: 265–81.
- Friedman JN, Goldman RD, Srivastava R, Parkin PC. Development of a clinical dehydration scale for use in children between 1 and 36 months of age. *J Pediatr* 2004; 145: 201–7.
- Bailey B, Gravel J, Goldman RD, Friedman JN, Parkin PC. External validation of the clinical dehydration scale for children with acute gastroenteritis. *Acad Emerg Med* 2010; 17: 583–8.
- Goldman RD, Friedman JN, Parkin PC. Validation of the clinical dehydration scale for children with acute gastroenteritis. *Pediatrics* 2008; 122: 545–9.
- Gravel J, Manzano S, Guimont C, Lacroix L, Gervais A, Bailey B. Multicenter validation of the clinical dehydration scale for children. *Arch Pediatr* 2010; 17: 1645–51.
- Karas J, Ashkenazi S, Guarino A, Lo Vecchio A, Shamir R, Vandenplas Y, et al. On behalf 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* 2015; 100: 359–63.
- Karas J, Ashkenazi S, Guarino A, Lo Vecchio A, Shamir R, Vandenplas Y, et al. On behalf of the Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT). Developing a core outcome measurement set for clinical trials in acute diarrhoea. *Acta Paediatr* 2016; 105: e176–80.
- Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr* 2014; 58: 531–9.
- Guarino A, Guandalini S, Lo Vecchio A. Probiotic for prevention and treatment of diarrhea. *J Clin Gastroenterol* 2015; 49Suppl: S37–45.
- Gregorio GV, Dans LF, Silvestre MA. Early versus Delayed Refeeding for Children with Acute Diarrhoea. *Cochrane Database Syst Rev* 2011; 7: CD007296.
- World Health Organization. *The Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers* – 4th rev. World Health Organization, 2005.
- MacGillivray S, Fahey T, McGuire W. Lactose avoidance for young children with acute diarrhoea. *Cochrane Database Syst Rev* 2013; 10: CD005433.
- Guarino A, Lo Vecchio A, Berni Canani R. Chronic diarrhoea in children. *Best Pract Res Clin Gastroenterol* 2012; 26: 649–61.
- Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012; 54: 136–60.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1 Conflicts of interest.