NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review of Clinical Guideline (CG84) – Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years

Background information

Guideline issue date: 2009

3 year review: 2012

National Collaborating Centre: Women's and Children's Health

Review recommendation

- The guideline should not be updated at this time.

Factors influencing the decision

Literature search

1. Through an assessment of abstracts from a high-level randomised controlled trial (RCT) search, new evidence was identified relating to the following clinical areas within the guideline:
    - Fluid management
    - Other therapies
2. Through this stage of the process, a sufficient number of studies (n=33) relevant to the above clinical areas were identified to allow an assessment for a proposed review decision.
3. From initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by members of the Guideline Development Group, as well as the high-level RCT search, an

additional focused literature search was conducted for the following clinical area:

- Is there a systematic scoring approach for the assessment of dehydration in children under 5 years of age?

4. The evidence and intelligence identified through the process suggests that two minor areas of the guideline may need updating at this stage:
    - anti-diarrhoeal agents
    - probiotics
5. Several ongoing clinical trials were identified (publication dates unknown) focusing on:
    - rehydration and electrolyte maintenance in children with gastroenteritis
    - oral ondansetron and dimenhydrinate in children with vomiting due to acute gastroenteritis
    - Filtrum-STI (lignin hydrolytic) in children with viral gastroenteritis
    - oral zinc for the treatment of acute diarrhoea in US children
    - probiotics in children with gastroenteritis

Guideline Development Group perspective

6. A questionnaire was distributed to GDG members to consult them on the need for an update of the guideline. Seven responses were received with five respondents stating that they do not think the guideline needs to be updated at this point in time, one respondent stating that the guideline should be updated and one respondent was unsure.
7. Three respondents highlighted that since the publication of the guideline, there has been relevant new literature on the following topics:
    - use of zinc, oral rehydration solution and pre/probiotics
    - rapid or ultra-rapid IV hydration
    - ondansetron (and other antiemetics including metoclopramide and domperidone) for gastroenteritis

- assessment of dehydration (using a systematic scoring approach)
- racecadotril to control diarrhoea in gastroenteritis

8. One respondent highlighted that there is a now a national, HPA led, British Paediatric Allergy, Immunology and Infectious Diseases Group endorsed guideline on the management of acute bloody diarrhoea in children.
9. With regard to ongoing research relevant to the guideline, one respondent stated that their group is planning an analysis of data comparing clinical assessment of hydration with urine dipstick specific gravity in pre-school children presenting with any illness to primary care and hope to make this available by mid 2013. Another respondent stated that they were aware of two trials in development in London and Wales but that they were at an early stage.
10. This feedback contributed towards the development of the clinical question for the focused search.

Implementation and post publication feedback

11. In total 23 enquiries were received from post-publication feedback, most of which were routine. Key themes emerging from more complex post-publication feedback all related to fluid management and included:
    - calculation of fluid deficit in relation to the weight of the child during fluid management (in children under 5 with diarrhoea and vomiting)
    - clarification of dosage recommendations relating to fluid replacement for a non-shocked child
    - clarification of recommendation on the rate of intravenous rehydration/rate of fluid deficit replacement
12. One implementation study from published literature was identified:
    - A review of the practice of diagnosis and management of gastroenteritis in children below years in two district general hospitals (Kunnath et al. 2010)

13. Qualitative input from the field team highlighted the following:
    - One person commented that the guideline has been very helpful for a group of health visitors in advising mothers of young children and in ensuring they are given consistent advice
    - Another person commented that the guideline was straightforward to implement
    - A third person commented that the guideline is “heavily” used by NHS Direct nurses and health advisors

Relationship to other NICE guidance

14. NICE guidance related to CG84 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
The guideline should not be considered for an update at this time.

15. In total 9 stakeholders commented on the review proposal during the 2 week consultation period (see Appendix 2).
16. Four stakeholders agreed with the review proposal recommendation that the guideline should not be updated at this time and three had no comments.
17. Two stakeholders did not agree:
    - One stakeholder made reference to two studies relating to anti-diarrhoeal agents that they suggested were not included in the review. However, one of these studies was included in the review consultation document, while the other study was not as it was published after the searches had already been done. This study relates to a small area of the guideline and there are a number of ongoing trials relating to other areas of the guideline that are expected to report in the next two to three years. It is therefore considered premature to update the guideline at this time. However, this information will be considered in the future update review of this guideline.

- One stakeholder commented that the guideline should be updated in view of the recent evidence that had been identified. However, it is considered to be premature to update the guideline at this time as only two minor areas of the guideline may need updating and there are a number of ongoing trials which are expected to report in the next two to three years.

Anti-discrimination and equalities considerations

18. No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The guideline addresses the diagnosis, assessment and management of children younger than 5 years with acute diarrhoea and vomiting caused by gastroenteritis in England and Wales.

Conclusion

19. The evidence and intelligence identified through the process suggests that two minor areas of the guideline may need updating at this stage:
    - anti-diarrhoeal agents
    - probiotics
20. However as these are minor areas and there are a number of ongoing trials which are expected to report in the next two to three years, it is considered to be premature to update the guideline at this time.

Relationship to quality standards

21. This topic is not part of the library of NICE Quality Standard NHS healthcare topics.
22. This topic is not currently related to a published quality standard or a quality standard in development.

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Centre for Clinical Practice
10 July 2012

Appendix 1

The following NICE guidance is related to CG84:

Guidance	Review date
CG116: Food allergy in children and young people: Diagnosis and assessment of food allergy in children and young people in primary care and community settings. February 2011.	To be confirmed
CG99: Constipation in children and young people: Diagnosis and management of idiopathic childhood constipation in primary and secondary care. May 2010.	May 2013
CG89: When to suspect child maltreatment. July 2009.	July 2012
CG86: Coeliac disease: Recognition and assessment of coeliac disease. May 2009.	May 2012
Related NICE guidance in progress	
The management of Crohn's disease (due October 2012)	To be confirmed

Appendix 2

National Institute for Health and Clinical Excellence

Review of Clinical Guideline (CG84) – Diarrhoea and vomiting in children under 5

Guideline Review Consultation Comments Table

28 May 2012–13 June 2012

Stakeholder	Agree with proposal to not update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
Abbott Laboratories	No	Regarding review of Section 8.2 anti-diarrhoeal agents. One additional study to those in the current guideline has been identified. This is the Lehert study which is a meta-analysis that includes data from eight relevant controlled trials. The main objective of the meta-analysis was to evaluate the efficacy of racecadotril as an adjunct to ORS compared to ORS alone, or ORS + placebo for the treatment of infants and children with acute diarrhoea. The meta-analysis used randomized controlled trials with individual patient data to: 1) Assess the overall efficacy of racecadotril + ORS compared with ORS alone, adjusting for relevant baseline conditions. 2) Homogenise the calculation of studied endpoints with the same definition across trials.			Thank you for your comment Lehert 2011 was one of the studies assessed and discussed in the consultation document. Through an assessment of abstracts, the document concluded that racecadotril may be useful in the

Stakeholder	Agree with proposal to not update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		3) Identify the baseline predictors of ORS therapy response out of consideration of treatment. 4) Test the invariance of efficacy to possible responder sub-groups and baseline conditions. The meta-analysis included all randomized controlled trials with randomised racecadotril administration as an adjunct to ORS, without restriction on language or publication, and characterised by an acceptable methodological quality (Chalmers Score >50). It included over 1,300 patients from eight randomized controlled trials that were conducted in a variety of different countries and therefore gathers the largest number of trials and patients in the study of racecadotril. Despite being conducted in different countries, heterogeneities were found between data in terms of inclusion criteria, baseline characteristics of patients and primary and secondary efficacy outcomes. The analyses were carried out both on the ITT population but also using the sample size as analysed in the original papers. A high proportion of patients completed the studies (1,238 patients, 89.5%). Of those patients not completing the studies, the reasons for discontinuation were: • AE (1.6%) • concomitant illness not related with diarrhoea (1.6%) • aggravation or hospitalisation (2.7%)			management of children with diarrhoea. With regard to your request to clarify which studies we refer to, the studies considered in the consultation document are referenced within the body text and references sections. The Rautenberg 2012 study was not included in the review consultation document as it was published after the searches had already been done. Overall, through the review process, we identified a number of

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		• parental withdrawal of consent for continuation (2.9%) • lost to follow-up (1.9%) No significant differences were observed between treatment groups in the reasons given for patient discontinuation, except for aggravation/hospitalisation (3.6% and 1.7% for ORS +/-placebo and racecadotril + ORS groups, respectively, p=0.029). Racecadotril was effective in reducing diarrhoea in terms of the three key efficacy outcomes; duration of diarrhoea, stool output and number of diarrhoeic stools. Racecadotril + ORS reduced stool output in inpatient studies (43% reduction compared with ORS +/- placebo), and number of diarrhoeic stools in outpatient studies (38% relative reduction compared with ORS +/- placebo). In terms of safety this study showed that the number of patients with AEs was not statistically different: 11.6% (81/698) in the racecadotril + ORS group and 10.1% (70/695) in ORS +/- placebo. The number of patients needed to harm (NNH) was 65 (SD, 29-125). The reason racecadotril safety was only briefly reported in this analysis was because it has been investigated elsewhere on a much wider scale in post-marketing analyses. Amongst 14.54 million paediatric patients, the individual case safety report occurrence was 1/338,000. Results from the post-marketing database showed the occurrence of AEs and			studies which revealed that two minor areas of the guideline (anti-diarrhoeal agents and probiotics) may need updating. However, we also considered that there are a number of ongoing trials that are expected to report in the next two to three years. Hence, it would be premature to update the guideline at this time. This information will be considered in the future update review of this guideline.

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		withdrawals due to AEs was not greater in patients treated with racecadotril + ORS compared with ORS +/- placebo. *Table 1: RCTs investigating racecadotril in paediatric patients with acute diarrhoea*			

Study author	Country	Study design and setting	Patient age (range) for study inclusion	Interventions	Primary outcome	Total patient number
Cézard 2001 (5)	France	RCT, placebo-controlled, inpatient	3-48 months	Racecadotril + ORS vs placebo + ORS	Stool output (g/hr and g/kg body weight) during 48 hours	168
Salazar-Lindo 2000 (13)	Peru	RCT, placebo-controlled, inpatient	3-35 months	Racecadotril + ORS vs placebo + ORS	Stool output (g/kg body weight) during 48 hours	135
Cojocaru 2002 (9)	France	RCT, open-label, outpatient	3-36 months	Racecadotril + RT vs RT alone	Number of additional consultations	164
Álvarez Calatayud 2009 (8)	Spain	RCT, cohort, outpatient	3-36 months	Racecadotril + ORS vs ORS alone	Number of diarrhoeic stools during 48 hours	148
Santos 2006 (14)	Spain	RCT, open-label, outpatient	3-36 months	Racecadotril + ORS vs ORS alone	Total number of diarrhoeic stools	179

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Gutiererez-Castrellon 2008 (15)	Mexico	RCT, placebo-controlled, inpatient	1-24 months	Racecadotril + ORS vs placebo + ORS	Stool output at 48 hours and throughout study	270
	Mexico	RCT, placebo-controlled outpatient	1-60 months	Racecadotril + ORS vs placebo + ORS	Total number of diarrhoeic stools at 48, 72 hours and throughout study duration	184
Savitha 2005 (11)	India	RCT, placebo-controlled, inpatient	3-60 months	Racecadotril + ORS vs placebo + ORS	Mean diarrhoea duration and ORS intake	60
Melendez Garcia 2007 (12)	Guatemala	RCT, outpatient	3-71 months	Racecadotril + ORS vs placebo + ORS	Total number of diarrhoeic stools	50

Abbreviations: g, grams; h, hour; ORS, oral rehydration solution; RCT, randomised controlled trial; RT, rehydration therapy; vs, versus.

Additionally there are other studies with racecadotril in children under 5 that should be included in the review. CAN YOU PLEASE CLARIFY WHICH STUDIES YOU ARE REFERRING TO?

A health economic study has also been published. The purpose of this analysis was to determine the cost-effectiveness of as an

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		adjunct to ORS versus ORS alone for infants and children aged 3 months to 11 years with acute diarrhoea in Scotland. The analysis considered the efficacy of racecadotril and ORS in preventing GP reconsultation; drug acquisition costs and costs of GP consultations and inpatient stays; the QoL impact associated with moderate and severe diarrhoea. Base-case results demonstrated that racecadotril as an adjunct to ORS dominates ORS alone for the treatment of acute diarrhoea in infants and children i.e. it is associated with lower costs and greater clinical benefits. Although racecadotril is associated with higher acquisition costs, there are incremental savings in GP reconsultation and referral costs. Extensive sensitivity analyses were conducted to test the impact of parameters in the model on the cost-effectiveness of racecadotril versus ORS alone and under most circumstances racecadotril continued to dominate ORS alone in children with acute diarrhoea. In summary, therefore, this economic evaluation demonstrates that racecadotril represents a cost-effective use of NHS resources in Scotland, a result which is largely robust to variations in parameters within the economic evaluation. The evidence presented demonstrates that racecadotril is a clinically and cost effective option for use as an adjunct to ORS for the treatment of acute diarrhoea in infants (older than 3 months), and in children, together with oral rehydration, and the usual support measures, when these measures alone are insufficient to control the clinical condition (as per the licensed			

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		indication). Taking the above into account the update of the anti-diarrhoeal area is not a minor consideration and the guideline should be updated with information regarding the use of racecadotril as it is a new treatment for diarrhoea in children above 3 months up to 4 years old with acute diarrhoea. References: Lehert P, Cheron G, Calatayud GA, Cezard JP, Castrellon PG, Garcia JM, et al. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. Dig Liver Dis. 2011 Sep;43(9):707-13. Rautenberg TA, Zerwes U, Foerster D, Aultman R. Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD model. ClinicoEconomics and Outcomes Research. 2012;4:109–16.			
British Society of Gastroenterology	No	Basically would agree with what they are suggesting (which is they are not going to review in detail as no new information and some trials due to report in the next year or two).			Thank you for your comment.
British Society of Paediatric	Yes	If further supportive data on ondansetron emerge, it may merit consideration of recommendation, in the circumstances of a child for whom ongoing vomiting may preclude ORS therapy.			Thank you for your comment.

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Gastroenterology Hepatology and Nutrition					Your point has been noted and will be considered in a future review of the guideline.
British Society of Paediatric Gastroenterology Hepatology and Nutrition		The volume of data showing a beneficial role for probiotics is increasing, and the findings are quite consistent. Although this treatment modality may not affect mortality or severe morbidity, there may be significant economic benefits for probiotics in reducing the duration of diarrhoeal episodes (eg allowing parents to return to work sooner).			Thank you for your comment. Your point has been noted and will be considered in a future review of the guideline.
Department of Health		No comments			Thank you for your comment.
GDG Member		As for the clinical issues, I was a keen advocate of including ondansetron in the first guideline, but due to safety concerns, the GDG felt unable to include it. I note new evidence further strengthening the case for the drug. HOWEVER, there is now an FDA warning over the use of this drug in certain high risk situations, e.g. where there may be electrolyte imbalance, as there is a risk of serious cardiac arrythmias. My own Trust has stopped us using ondansetron in acute gastroenteritis as a result.			Thank you for your comment. Your point has been noted and will be considered in a future review of the guideline.

Stakeholder	Agree with proposal to not update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
GDG member	Disagree – should be updated based on recent evidence	Further search on use of probiotics, zinc I priobiotics, antidiarrhoeals,(iracecaditric, diosmectite) and nitazoxamide			Thank you for your comment. Through the review process we identified a number of studies which revealed that two minor areas of the guideline (anti-diarrhoeal agents and probiotics) may need updating. However, we also considered that there are a number of ongoing trials that are expected to report in the next two to three years. Hence, it would be premature to update the guideline at this time.
Lancashire Care NHS Foundation Trust	Yes	We agree it shouldn't be updated at this time, but reviewed again in 3 years.			Thank you for your comment.

Stakeholder	Agree with proposal to not update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
NHS Direct	Yes	No further comments			Thank you for your comment.
Royal College of Nursing		No comments			Thank you for your comment.
Royal College of Radiologists		No comments			Thank you for your comment.