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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Assessment of Dehydration and Oral Rehydration Therapy for Pediatric Patients with Dehydration: A Review of Clinical Effectiveness, Clinical Utility, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	March 16, 2020
Report Length:	22 Pages

CADTH

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Cite As: Assessment of dehydration and oral rehydration therapy for pediatric patients with dehydration: a review of clinical effectiveness, clinical utility, and guidelines. Ottawa: CADTH; 2020 Mar. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

CPG	clinical practice guideline
IDSA	Infectious Disease Society of America
IQR	interquartile range
ORS	oral rehydration solution
ORT	oral rehydration therapy
WHO	World Health Organization

Context and Policy Issues

Dehydration occurs when the body uses up or loses more fluid than it takes in, and this can have a negative impact on normal functioning.[1] Dehydration often results from gastroenteric diseases involving vomiting, diarrhea, or both.[2] Dehydration may also be associated with other conditions such as diabetic ketoacidosis, excessive sweating, and burns.[2] Globally, diarrhea is one of the leading causes of mortality and morbidity in the pediatric population; particularly those living in areas of the world with limited resources, and young children (under 5 years old).[2,3] In children, dehydration is characterized as mild (3% to 5% weight loss), medium (6% to 10% weight loss), or severe (10% to 15% weight loss).[4] Children below the age of 12 years have a higher body water content (60% to 80%) compared with adolescents or adults (55% to 60%) and are more prone to dehydration during illness.[4]

Theoretically, it seems that knowledge of the degree of dehydration would likely assist in guiding treatment decisions for managing dehydration.[5] Assessment of weight loss is considered as the gold standard for accurate determination of the extent of dehydration.[5,6] However, in clinical practice, the baseline or pre-illness weight is rarely available, therefore loss of weight at presentation is difficult to assess.[6] Hence, other signs and symptoms have been considered to assess the extent of dehydration. These include sunken eyes, skin turgor (skin elasticity), lack of tears, urine output, mucous membrane appearance, capillary refilling time, heart rate, and respiratory rate.[6] A number of scoring tools based on signs and symptoms are available, such as Clinical Dehydration score (CDS), Gorelick scale, and WHO scale.[5,7,8] These scales appear to have limited ability to diagnose dehydration.[5,9]

There appears to be uncertainty regarding the clinical utility of these dehydration assessment tools and consequently deciding on the best treatment method is sometimes difficult. Underestimation of dehydration can lead to inadequate treatment resulting in increased morbidity or mortality, whereas overestimation can result in unnecessary hospitalization and treatment involving increased complications and resource use.[8] Treatment for dehydration includes administration of fluids either orally or intravenously. Generally, oral rehydration therapy (ORT) is used in case of mild to moderate dehydration and intravenous therapy for severe dehydration.

The purpose of this report is to review the clinical utility of tools to assess dehydration in pediatric patients, and the clinical effectiveness of the methods of administration of oral rehydration therapy (ORT) in pediatric patients. A recent CADTH report[10] provides information on the comparative clinical effectiveness of oral rehydration solutions (ORSs) used for ORT, hence ORSs will not be discussed in this current report. Additionally, this

report aims to review the evidence-based guidelines regarding assessment of dehydration and ORT in pediatric patients.

Research Questions

1. What is the clinical utility of diagnostic tools for assessing dehydration in pediatric patients?
2. What is the clinical effectiveness of methods of administration of oral rehydration therapy dehydration in pediatric patients?
3. What are the evidence-based guidelines regarding assessment of dehydration in pediatric patients?
4. What are the evidence-based guidelines regarding oral rehydration therapy in pediatric patients?
5. What are the evidence-based guidelines regarding oral rehydration therapy in pediatric patients in an at-home setting by parents or caregivers?

Key Findings

Two guidelines recommend oral rehydration therapy for mild to moderated dehydration in pediatric patients (strong recommendation, moderate to high level evidence). One guideline also recommends use of antiemetic agents such as ondansetron to facilitate tolerance of oral rehydration therapy in children (older than four years) and adolescents with acute gastroenteritis associated with vomiting (weak recommendation, moderate level evidence). One systematic review of 15 guidelines reported that the guidelines recommend oral rehydration therapy as first-line treatment in pediatric patients with acute gastroenteritis and moderate dehydration (strength of recommendation: not reported, level of evidence mostly moderate).This systematic review also reported that the guidelines recommend assessment of dehydration based on signs and symptoms (strength of recommendation not reported; level of evidence low or not reported), and a few of these guidelines recommend use of scoring systems.

Findings need to be interpreted in the light of limitations such as sparse reporting of methodological details and evidence supporting the recommendations.

No relevant evidence on the comparative clinical utility of diagnostic tools for assessing dehydration was identified, therefore a summary cannot be provided.

No relevant evidence on the comparative clinical effectiveness of methods of administration of oral rehydration therapy in pediatric patients was identified.

No evidence-based guideline providing recommendation regarding oral rehydration therapy in pediatric patients in an at-home setting by parents or caregivers was identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and

Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were oral rehydration therapy in pediatrics and diagnostic/assessment tools. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta analyses, randomized controlled trials, non-randomized studies, and guidelines. The search was also limited to English language documents published between January 1, 2015 and February 13, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pediatric patients under 18 years with, or at risk of, mild to moderate dehydration from any cause
Intervention	Q1,3: Diagnostic tools for assessing dehydration (e.g., GULP dehydration risk screening tool, skin pinch [turgor test], Clinical Dehydration Scale (CDS), the World Health Organization (WHO) scale, and the Gorelick scale) Q2: Methods and rate of administration of oral hydration therapy (e.g., teaspoon every 2 minutes, mL multiplied by weight of patient over 4 hours, 100 ml every 5 minutes) Q4-5: Oral rehydration therapy (e.g., all forms, including water, juice, milk, oral rehydration solutions [such as electrolyte solutions, Pedialyte])
Comparator	Q1: Other diagnostic tools; no diagnostic tools Q2: Other methods or rates of administration Q3-5: Not applicable
Outcomes	Q1: Clinical utility (e.g., weight changes, changes in symptoms, appropriate treatment) Q2: Clinical effectiveness (e.g., weight changes, changes in symptoms, safety) Q3-4: Guidelines (e.g., guidelines regarding administration, dosage, type, and selection of oral rehydration therapy, guidelines on who can administer oral dehydration therapy, guidelines regarding diagnosis or diagnostic tools for dehydration; guidelines regarding administration of ondansetron with oral rehydration therapy) Q5: Guidelines on administration of oral rehydration therapy by parents or caregivers, guidelines on administration of oral rehydration therapy in an at-home setting
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Articles reporting on accuracy of diagnostic tools were excluded, unless clinical utility outcomes were reported. Articles comparing oral rehydration solutions were excluded, as these were discussed in a separate CADTH report.[10] Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by one reviewer using the AMSTAR 2 tool,[11] the non-randomized study was critically appraised using the Downs and Black checklist,[12] and the guidelines were assessed with the AGREE II instrument.[13] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 829 citations were identified in the literature search. Following screening of titles and abstracts, 813 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these 17 potentially relevant articles, 13 publications were excluded for various reasons, and four publications met the inclusion criteria and were included in this report. These comprised one systematic review of guidelines[14] and two evidence-based guidelines.[15,16] No relevant health technology assessments or randomized controlled trials were identified. No relevant articles related to questions 1, 2, and 5 were identified. Appendix 1 presents the PRISMA[17] flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized and additional details are provided in Appendix 2; Table 2 (systematic review); and Table 3 and Table 4 (guidelines). One systematic review of guidelines[14] and two evidence-based guidelines[15,16] were included.

Study Design

The systematic review[14] was a systematic review of 15 clinical practice guidelines published between 2005 and 2014.

For both included guidelines,[15,16] the guideline development group comprised a multidisciplinary team (experts in areas such as infectious diseases, gastroenterology, and epidemiology); a systematic literature search was conducted to identify evidence; and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used for assessing quality of evidence and strength of recommendations. In one guideline[15] the recommendations were formulated using open-ended discussions and in the other guideline[16] the method used to formulate the recommendation was not mentioned.

Country of Origin

The first author of the systematic review[14] of guidelines was from Italy, and the systematic review assessed clinical practice guidelines (CPGs) from several organizations and countries, including both high-income and low-income countries. Of the included guidelines in this systematic review, one guideline was Canadian, produced by the Canadian Pediatric Society.

Of the two guidelines, one guideline[15] was from China, and the other guideline[16] was by the Infectious Disease Society of America (IDSA).

Patient Population

The systematic review[14] of guidelines was related to pediatric patients with acute gastroenteritis. Of the 15 included CPGs, eight CPGs included patients younger than 5 years; one clinical practice guideline (CPG) included patients older than 3 months; one CPG included patients under 18 years of age; one CPG included infants; one CPG included infants and children, and 3 CPGs did not provide specifics of the pediatric patients.

In one guideline[15] the target population was children with acute infectious diarrhea in China. In this guideline the intended users were not explicitly stated but it appears to be intended for health professionals in China. In the other guideline[16] the target population was children and adults with suspected or confirmed diarrhea and the intended users were healthcare professionals.

Interventions and Comparators

The systematic review[14] of guidelines discussed several interventions for the management of dehydration. These included techniques for assessing dehydration, routes of administration used for rehydration, and oral rehydration solutions. Only interventions relevant for this report are considered here.

One guideline[15] examined rehydration therapy (relevant intervention for this current report) as well as other interventions including treatment with probiotics, zinc supplementation, and antibiotics. The other guideline[16] examined rehydration therapy (relevant intervention for this current report) as well as other interventions including treatment with probiotics, zinc supplementation, antiemetic agents (such as ondansetron), and antibiotics.

Outcomes

The systematic review[14] of guidelines presented a summary of recommendations from the various guidelines with respect to assessment of dehydration and ORT.

Both guidelines[15,16] presented recommendations for ORT. Outcomes considered in one guideline[16] included rehydration status, weight gain, and duration of diarrhea. Another guideline[15] did not report on outcomes that were considered.

Summary of Critical Appraisal

The critical appraisal of the included studies is summarized below and details are presented in Appendix 3; Table 5 (systematic review), and Table 6 (guidelines).

In the included systematic review[14] of guidelines the objective was clearly stated, a comprehensive literature search was conducted, a flow-chart of the study selection was presented, and a list of included studies (i.e., guidelines) was provided. The authors mentioned that there were no conflicts of interest. A list of excluded guidelines was not provided. Also, it was unclear if the selection of guidelines and data extraction were done in duplicate, if quality assessment had been conducted, or if publication bias had been explored. Additionally, the supporting evidence for the guideline recommendations was not presented. Under these circumstances, it is difficult to ascertain the quality of the included guidelines, and if all relevant evidence was considered; and the basis on which the recommendations were made is unclear. Hence it is difficult to judge the reliability of the recommendations presented.

In both guidelines[15,16] the objective was described, the target population was specified, the guideline development group comprised of experts in multidisciplinary areas, a systematic literature search was conducted, and the recommendations were clearly presented. In one guideline[16] the intended user was described and the criteria for selecting evidence was described, and in another guideline[15] the intended user was apparent but not explicitly described and the criteria for selecting evidence were not described. In one guideline[15] the methods for formulating recommendations were stated and the guideline was externally reviewed, and for another guideline[16] the method of formulating the recommendations and whether it was externally reviewed were unclear. In one guideline[16] supporting evidence was described to some extent and a method for updating the guideline was described; and in another guideline[15] these were not described. In one guideline[16] it was mentioned that conflicts of interest had been recorded and addressed; and in another guideline[15] it was unclear, hence potential for bias cannot be ruled out. In both guidelines[15,16] it was unclear if the views and preferences of the patient or general population had been sought; the strengths and limitations of the health benefits, adverse effects, and risks had been considered; and factors relating to applicability (such as facilitators and barriers, provision of tools, resource implications, and monitoring) had been considered.

Summary of Findings

Relevant study findings are summarized and details of the main study findings and authors' conclusions are presented in Appendix 4; Table 7 (systematic review), and Table 8 (guidelines).

Clinical Utility of Diagnostic Tools

No relevant evidence on the comparative clinical utility of diagnostic tools for assessing dehydration was identified, therefore a summary cannot be provided.

Clinical Effectiveness of Methods of Administration

No relevant evidence on the comparative clinical effectiveness of methods of administration of oral rehydration therapy in pediatric patients was identified, therefore a summary cannot be provided.

Guidelines

Two evidence-based guidelines,[15,16] were identified that provided recommendations for ORT. In addition, one systematic review,[14] of guidelines summarized recommendations from 15 guidelines regarding assessment of dehydration and ORT.

Guideline on dehydration assessment

The systematic review[14] of 15 guidelines reported that assessment of dehydration using signs and symptoms was recommended by guidelines; in addition, a few (30%) of these guidelines recommended use of a scoring system, but the scoring system was not specified (strength of recommendations was not reported, level of evidence was generally low or not reported). Evidence on which the recommendations were based was not provided.

Guidelines on oral rehydration therapy

One guideline[15] recommends ORT, using WHO ORS or hypotonic ORS in case of mild to moderate dehydration in pediatric patients (recommendation: strong; evidence level: A [indicating high]). Evidence on which the recommendations were based was not provided. Another guideline[16] recommends ORS as the first line therapy for mild to moderate

dehydration in infants, children and adults with acute diarrhea from any cause (recommendation: strong, evidence level: moderate). The recommendation did not specify the types of ORS. This guideline also recommends ORS as the first line therapy for individuals with mild to moderate dehydration resulting from vomiting or severe diarrhea (strength of recommendation, and level of evidence were not reported). It also recommends use of antinausea and antiemetic agents such as ondansetron to facilitate tolerance of ORT in children (older than four years) and adolescents with acute gastroenteritis associated with vomiting (recommendation: weak, evidence level: moderate) Evidence on which the recommendations were based are presented in Table 8.

The systematic review[14] of 15 guidelines reported that the guidelines recommend the administration of ORS as first-line treatment for pediatric patients with acute gastroenteritis and moderate dehydration (strength of recommendation was not reported, level of evidence was mostly moderate). Hypo-osmolar ORS (sodium concentration 45 to 60 mmol/L) was recommended by 11 guidelines and low osmolality ORS (sodium concentration 75 mmol/L) was recommended by nine guidelines. Evidence on which the recommendations were based was not provided.

Guidelines on oral rehydration therapy in an at-home setting

No evidence-based guideline providing recommendations regarding ORT in pediatric patients in an at-home setting by parents or caregivers was identified, therefore a summary cannot be provided.

One guideline[15] mentioned (not presented as a recommendation and no supporting evidence) that for children with acute infectious diarrhea, and without dehydration or with mild dehydration, can be treated at home after receiving advice from the medical staff.

Limitations

The systematic review[14] of guidelines did not report on relevant items such as the quality of the included guidelines, the methodology that was used to produce the guideline reports, and the supporting evidence for the recommendations. In the two included guidelines[15,16] the supporting evidence was either not reported or the link between the evidence and the recommendation was not always clear.

The findings need to be interpreted with caution, considering the limitations mentioned.

No relevant evidence on the comparative clinical utility of diagnostic tools for assessing dehydration was identified, therefore a summary cannot be provided.

No relevant evidence on the comparative clinical effectiveness of methods of administration of oral rehydration therapy in pediatric patients was identified

No evidence-based guideline providing recommendation regarding ORT in pediatric patients in an at-home setting by parents or caregivers was identified

Conclusions and Implications for Decision or Policy Making

One systematic review of guidelines[14] and two evidence-based guidelines[15,16] were included.

Two guidelines[15,16] recommend ORT using ORS in cases of mild to moderate dehydration in pediatric patients (strong recommendations, moderate to high level evidence). One

guideline[16] also recommends use of antiemetic agents such as ondansetron to facilitate tolerance of ORT in children (older than four years) and adolescents with acute gastroenteritis associated with vomiting (weak recommendation: moderate level of evidence) Also, one systematic review[14] of 15 guidelines reported that the guidelines recommend ORT using ORS for moderate dehydration in pediatric patients (strength of recommendation not reported, level of evidence mostly moderate). This systematic review[14] also reported that the guidelines recommend assessment of dehydration using signs and symptoms (strength of recommendation not reported, level of evidence low or not reported); in addition a few (30%) of the guidelines recommend use of a scoring system.

No relevant evidence on the comparative clinical utility of diagnostic tools for assessing dehydration was identified, therefore a summary cannot be provided.

No relevant evidence on the comparative clinical effectiveness of methods of administration of oral rehydration therapy in pediatric patients was identified, therefore a summary cannot be provided.

No evidence-based guideline providing recommendation regarding ORT in pediatric patients in an at-home setting by parents or caregivers was identified, therefore a summary could not be provided.

One observational study,[18] reporting on the clinical utility of a tolerance test to identify dehydrated pediatric patients who are likely to benefit with ORT, did not meet the inclusion criteria for this report as there was no comparator group. However, it may provide some useful insights, so is discussed here. Patients who could tolerate over a 2-hour period, a drink of median volume 24.4 mL/kg (interquartile range, 12.5 mL/kg to 28.8mL/kg) when presented at the children's emergency department were considered eligible for home ORT. This study showed that 80% of the patients who passed this tolerance test, had improvement (adequately hydrated and reduced diarrhea) with home ORT. However, it was unclear how the cut-off point for the tolerance test had been determined.

Further research with well-designed studies to investigate the clinical utility of scoring systems and tests for assessing dehydration, may provide more insights into the appropriate methods for detecting the level of dehydration that will assist in deciding the best treatment option.

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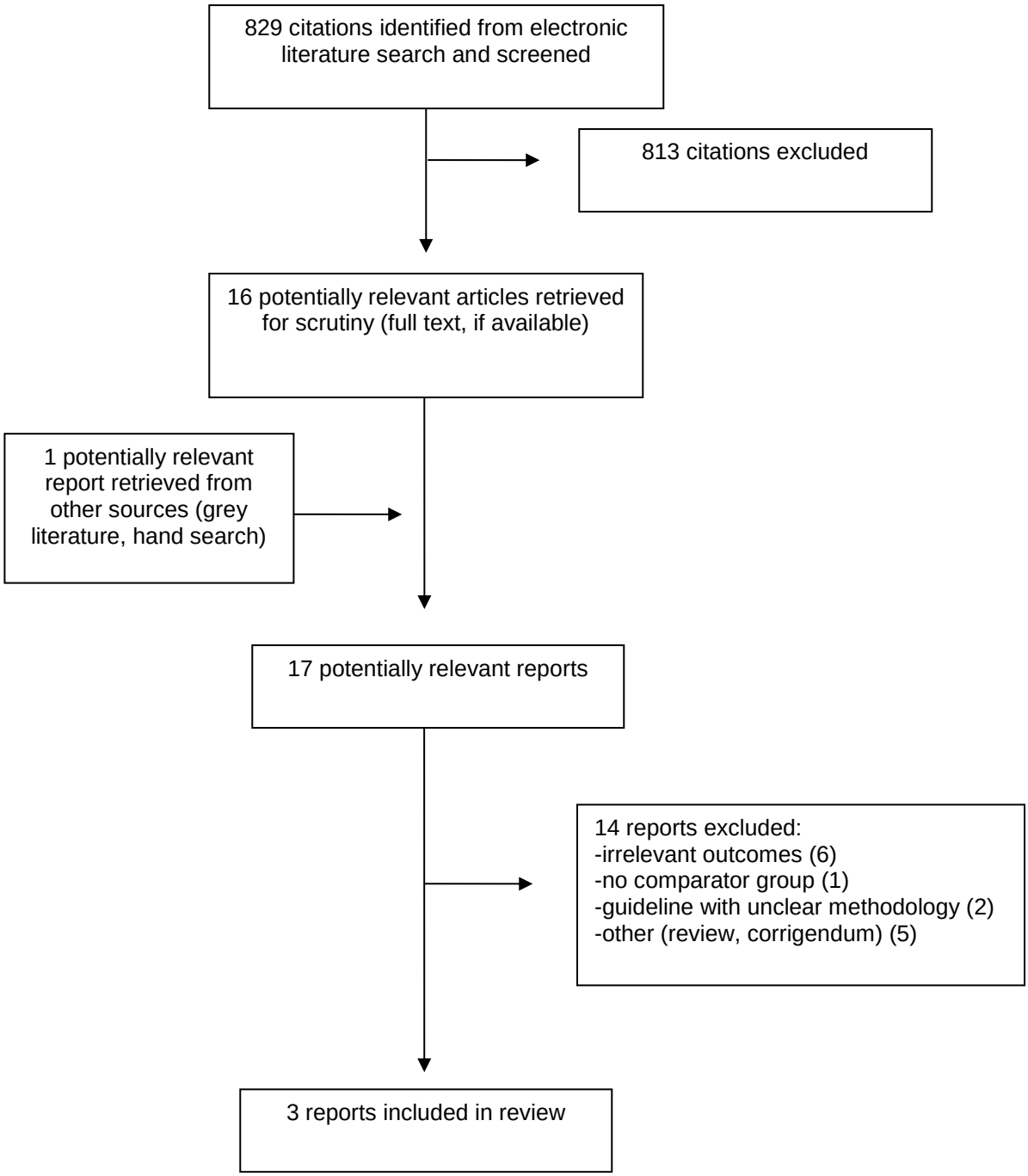
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2 : Characteristics of Included Systematic Review

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Lo Vecchio,[14] Italy, 2016	Systematic review of clinical practice guidelines. It included 15 CPGs published between 2005 and 2014 from various countries and by various organizations. These CGPs comprised: 2 from Australia, one each from Latin America, Kenya, Botswana, South Africa, India, Malaysia, China, Canada, US (CCHMC), UK (NICE), ESPGHAN, WGO, and WHO 6 CPGs related to HIC, 8 CPGs related to LIC, and 1 CPG related to both HIC and LIC (classified according to the International Monetary Fund list of countries) Aim: To systematically review CPGs on AGE to compare recommendations and provide a basis for developing universal recommendations for managing pediatric patients with gastroenteritis, that can be used globally	Pediatric patients with acute gastroenteritis Age: < 5 years (8 CPGs), > 3 months (1 CPG), < 18 years (1 CPG), infants (1 CPG), infants and children (1 CPG), not reported (3 CPGs)	Several interventions for management of dehydration. These included: techniques for assessing dehydration, routes of administration used for rehydration, oral rehydration solutions, diet, and medication. Setting: outpatient and inpatient (14 CPGs), and outpatient (1 CPG)	Recommendations

AGE = acute gastroenteritis; CCHMC = Cincinnati children's hospital medical center; CPG = clinical practice guideline; CPGs = clinical practice guidelines, ESPGHAN = European society or pediatric gastroenterology, hepatology, and nutrition; HIC = high income country; LIC = low income country; NICE = National Institute of Health and Care Excellence; WGO = World gastroenterology organization; WHO = World health organization.

Table 3 : Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Systematic review of Guidelines						
Lo Vecchio,[14] Italy, 2016						
As this was a systematic review of guidelines, characteristics are presented in Table 2.						
Guidelines						
Chen,[15] 2018, China						
Intended user: Target population: Pediatric patients with acute infectious diarrhea (in China)	Method/procedure for diagnosis, management, and prevention of acute infectious diarrhea in children Oral rehydration therapy (relevant for this report). Also, other treatments (not relevant for this report) included intravenous rehydration treatment, treatment with probiotics, zinc supplementation, and antibiotics	Clinical parameters relevant for patients with diarrhea such as dehydration status, duration of diarrhea, and stool character. Also, identification of pathogens if needed	Systematic literature search was conducted. Databases included PubMed, Embase, Cochrane, and China Biomedical database and were searched up to June 2013 Evidence selection and synthesis were not described	GRADE was applied to assess the quality of evidence and develop recommendations. The quality of evidence was categorized as high, moderate, low and very low. The strength of recommendations was categorized as strong or weak	Preliminary recommendations were formulated and then finalized using open-ended discussions. The guideline development group comprised experts in pediatric gastroenterology, pediatric infectious disease, and epidemiology	Published in a peer-reviewed journal
Shane (IDSA),[16] 2017, US						
Intended user: healthcare professionals Target population: children and adults with suspected or confirmed diarrhea	Methods/procedures for diagnosis and management of infectious diarrhea Oral rehydration therapy (relevant for this report). Also, other strategies (not relevant for this report) included diagnostic tests; intravenous rehydration treatment, antibacterial treatment; ancillary treatment with antimotility, antinausea, or	Clinical parameters relevant for patients with diarrhea such as dehydration status, weight gain, and duration of diarrhea. Also, identification of pathogens; strategies for preventing transmission of pathogens	Systematic literature search was conducted. Medline and Embase databases were searched between January 2000 to 31 December 2013 During the final preparation stage of the report data published after 1 January 2014 were also considered Evidence selection and	GRADE was applied to assess the quality of evidence and develop recommendations. The quality of evidence was categorized as high, moderate, low and very low. The strength of recommendations was categorized as strong or weak.	Method used to produce the recommendations was not stated. The guideline panel comprised of multidisciplinary experts in the areas of clinical medicine, infectious disease, epidemiology, preventive medicine, nutrition, microbiology, and enteric disease.	The guideline was reviewed and approved by IDSA SPGC and board of directors. Unclear if externally reviewed

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
	antiemetic agents; probiotics; or zinc for treatment or prevention.		synthesis were not described It was mentioned that the process of developing the guidelines was according to the handbook of clinical practice guideline development,[19] which included the GRADE method.			

GRADE = grading of recommendations assessment, development, and evaluation; IDSA = infectious disease society of America; SPGC = Standards and practice guidelines committee

Table 4: Method of Assessment of Evidence Levels and Recommendation Strengths

Assessment of Evidence Level	Assessment of Recommendation Strength
Chen,[15] 2018, China	
The authors used the Oxford evidence classification and Sacketts criteria (References[20,21] cited by the authors). "A: Evidence from a systematic review or meta-analysis of a homogeneous randomized controlled trial (RCT) or single RCT; B: evidence from multiple high-quality cohort studies, multiple high-quality cohort studies, single high-quality case–control studies or poor-quality single randomized controlled trials; C: evidence from large sample cases, poor quality single cohort studies or case–control studies; D: evidence from expert opinions." (p. 430)	"Highly recommended: evidence level A or B, and the benefits are very obvious; Recommendation: evidence level B and the benefits are obvious, or high-quality research (evidence level C) is not possible under certain conditions but the benefits are obvious; considered: with suspicious evidence quality or beneficial is not obvious; Not recommended: lack of evidence and the benefits are not obvious." (p. 430)
Shane (IDSA),[16] 2017, US	
Evidence level based on GRADE: Evidence from randomized trials is initially considered to be of high level and evidence from observational studies is initially considered to be of low level. However, the level of evidence is lowered or raised depending on several factors such as biases and extent of effect, and finally the evidence is graded as high, moderate, low or very low.	Strong recommendation and its implication: "Population: Most people in this situation would want the recommended course of action and only a small proportion would not Healthcare workers: Most people should receiver the recommended course of action Policy makers: The recommendation can be adapted as a policy in most situations" (p. e57)

Assessment of Evidence Level	Assessment of Recommendation Strength
	Weak recommendation and its implications: “Population: The majority of people in this situation would want the recommended course of action, but many would not Healthcare workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making Policy makers: There is need for substantial debate and involvement of stakeholders” (p. e57)

GRADE = grading of recommendations assessment, development, and evaluation.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2 tool11

Strengths	Limitations
Lo Vecchio,[14] 2016, Italy	
• The objective was clearly stated. This was a systematic review of CPGs • Multiple databases (PubMed, Cochrane library, and National Guideline Clearing House) were searched between January 2005 and May 2015. In addition, websites of societies and organizations that produce and/or endorse CPGs were searched. Experts in the field were consulted for additional documents. • Study selection was described, and a flow chart was presented • A list of included studies (i.e., guidelines) was provided • Characteristics of the included articles (guidelines) were presented but studies providing the evidence were not described • The authors mentioned that there were no conflicts of interest	• A list of excluded studies (i.e., guidelines) was not provided • Unclear if selection was done in duplicate • Unclear if data extraction was done in duplicate • Unclear if quality assessment was conducted • Unclear if publication bias was examined

Table 6: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline	
	Chen,[15] 2018, China	Shane (IDSA),[16] 2017, US
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	yes	yes
2. The health question(s) covered by the guideline is (are) specifically described.	Apparent but not explicitly described	yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	yes	yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	yes	yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	NR	NR
6. The target users of the guideline are clearly defined.	Apparent but not explicitly described	yes
Domain 3: Rigour of Development		

Item	Guideline	
	Chen,[15] 2018, China	Shane (IDSA),[16] 2017, US
7. Systematic methods were used to search for evidence.	Yes (Systematic literature search).	Yes (Systematic literature search)
8. The criteria for selecting the evidence are clearly described.	no	yes
9. The strengths and limitations of the body of evidence are clearly described.	NR	NR
10. The methods for formulating the recommendations are clearly described.	yes	NR
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	unclear	unclear
12. There is an explicit link between the recommendations and the supporting evidence.	unclear	to some extent (evidence was presented but the links between the evidence and recommendations were not always clear)
13. The guideline has been externally reviewed by experts prior to its publication.	yes	unclear
14. A procedure for updating the guideline is provided.	NR	yes
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	yes	yes
16. The different options for management of the condition or health issue are clearly presented.	yes	yes
17. Key recommendations are easily identifiable.	yes	yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	NR	NR
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	NR	NR
20. The potential resource implications of applying the recommendations have been considered.	NR	NR
21. The guideline presents monitoring and/or auditing criteria.	NR	NR
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	No funding	unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Unclear (It was mentioned that no financial or non-financial benefits were received related to the subject of the article)	COI recorded; and addressed on a case by case basis

COI = conflict of interest; NR = not reported.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings of Included Systematic Review

Main Study Findings	Authors' Conclusion
Lo Vecchio,[14] 2016, Italy	
Evidence on which the recommendations in the guidelines were based was not presented. The 15 included guidelines reported on various aspects of management of AGE. The aspects of relevance for this current report are reported here; these include assessment of dehydration and oral rehydration therapy. <u>Assessment of dehydration</u> Most guidelines (proportion not specified) mentioned that the loss of body weight was the most accurate indicator of presence and severity of dehydration. However, in clinical practice, the pre-illness weight is rarely available hence loss of weight at presentation is difficult to assess. Several parameters (clinical signs and symptoms) are used as an indirect measure of dehydration. Of these, the parameters commonly mentioned by the guidelines to assess dehydration were skin turgor (in 80% of the guidelines); sunken eyes (in 73.3% of the guidelines); general appearance (in 66.6% of the guidelines); and capillary refill time (in 60% of the guidelines); and mucous membranes (in 60% of the guidelines). The parameters (respiratory pattern, thirst, tears, urine output, radial pulse heart rate, extremities, metabolic acidosis, and sunken anterior fontanelle were mentioned less frequently in the guidelines (≤40%). Assessment of various dehydration signs and symptoms were recommended by the guidelines. It was mentioned that for one guideline the recommendation was based on strong evidence; for eight guidelines the recommendations were based on low evidence; and for six guidelines the level of evidence or the supporting evidence were not reported. Five guidelines recommended the use of scoring systems. It was mentioned that for one guideline the recommendation was based on low evidence; for one guideline the recommendation was based on very low evidence; and for three guidelines the level of evidence or the supporting evidence were not reported. Three of these guidelines recommended use of the CDS. <u>Oral rehydration therapy</u> All the guidelines recommended the administration of ORS as the first line treatment. Eleven CPGs recommended use of hypo-osmolar ORS (sodium concentration 45 to 60 mmol/L); and nine CPGs recommended low osmolality ORS (sodium concentration 75 mmol/L). Four CPGs mentioned the WHO solution with sodium concentration 90 mmol/L) and two CPGs mentioned use of Super ORS (i.e., ORS with micronutrients added to increase efficacy).	The authors concluded that "Key recommendations for the management of AGE in children are similar in CPGs. Together with accurate review of evidence-base this may represent a starting point for developing universal recommendations for the management of children with AGE worldwide." (p.2)

Main Study Findings	Authors' Conclusion
It was mentioned that for two guidelines the recommendation regarding the administration of ORS as a first-line treatment was based on strong evidence; for eight guidelines the recommendation was based on moderate evidence; for one guideline the recommendation was based on low evidence; and four guidelines the level of evidence or the supporting evidence were not reported. Evidence classification Relevant recommendations are summarized in Table 8	

Evidence classification	Classification system and terminology		Data source of evidence
	GRADE	Muir-Gray & Cook	
Strong	High level	I	Meta-analysis and more than one RCT
Moderate	Moderate level	II	RCT
Low	Low level	III	Cohort and observational studies
Poor	Very low level	IV or V	Case series, case report, and expert opinion

AGE = acute gastroenteritis; CDS = clinical dehydration scale; CPG = clinical practice guideline; CPGs = clinical practice guidelines; ORS = oral rehydration therapy.

Table 8: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Systematic Review of Guidelines	
Lo Vecchio,[14] 2016, Italy	
Assessment of dehydration Evidence: Evidence on which the recommendations were based was not presented however the strength of evidence was stated. Recommendation: Assessment of dehydration using signs and symptoms was recommended by the guidelines. Few (30%) of the guidelines recommended use of a scoring system. **Oral rehydration therapy** All the guidelines recommended the administration of ORS as first line treatment	**Assessment of dehydration** Strength of evidence: generally low or not reported Strength of recommendation: not reported **Oral rehydration therapy** Strength of evidence: variable (mostly moderate), Strength of recommendation: not reported

Recommendations	Strength of Evidence and Recommendations
(As this was a systematic review of guidelines, details are available Table **7**)	(As this was a systematic review of guidelines, details are available Table 7)
Guidelines	
Chen,[15] 2018, China	
Oral rehydration therapy Evidence: The authors mentioned that for acute infectious diarrhea, ORT is as effective as IVT, and that ORT is both clinically effective and cost effective (based on two reports by (1) WHO and (2) ESPGHAN/ ESPID) Recommendation: "Oral rehydration using WHO-oral rehydration solution (ORS) or hypotonic ORS is recommended for mild or moderate dehydration (evidence level A)." (p. 431) --- **Home treatment** The guideline mentioned (i.e., did not present it as a recommendation rather as a general principle) the following principles of treating acute infectious diarrhea at home (however no supporting evidence or level of evidence was presented). "Children without dehydration and mild dehydration can be treated at home, and medical staffs should advise parents to stick to the following principles when treating children at home: (1) give the child enough fluid to prevent dehydration; (2) give zinc supplements; (3) resume feeding as soon as possible. Advise the parents to take the children to the hospital as soon as possible when the conditions of diarrhea are not improved or with any of the following symptoms (1) severe diarrhea, frequent stools or large amount of diarrhea; (2) cannot eat normally; (3) frequent vomiting, cannot be orally administered; (4) high fever (< 3 months old, > 38 °C; > 3 months, > 39 °C); (5) appearance of dehydration: obvious thirsty, sunken eye, irritability and lethargy; (6) blood in the stool; (7) age < 6 months, with a history of chronic disease, and with complications." (p. 433-434)	**Oral rehydration therapy** Strength of evidence: A Strength of recommendation: The authors mentioned that oral rehydration was strongly recommended for preventing dehydration and treating mild or moderate dehydration. In China, hypotonic ORS is highly recommended. --- **Home treatment** Strength of evidence: not reported Strength of recommendation: not applicable (as it was not stated as a recommendation rather as a general principle).
Shane (IDSA),[16] 2017, US	
Oral rehydration therapy Evidence: According to one report, ORT is useful for managing dehydration in all age groups irrespective of the cause and is recommended as first-line therapy. A systematic review involving children (age < 5 years) experiencing dehydration resulting from diarrhea, arising from any cause, showed that reduced osmolarity ORS was associated with fewer unscheduled infusions compared with WHO-ORS. A systematic review involving children (age <18 years) showed that there were no important clinical differences between ORT and IVT, in terms of failure to rehydrate, weight gain at discharge, hyponatremia or hypernatremia, duration of diarrhea, or total fluid intake. Also, it was estimated that 4% of children receiving ORT may fail treatment and require IVT.	**Oral rehydration therapy** *For mild to moderate dehydration associated with acute diarrhea* Strength of evidence: moderate Strength of recommendation: strong *For mild to moderate dehydration associated with vomiting or severe diarrhea* Strength of evidence: not reported Strength of recommendation: not reported *For maintenance* Strength of evidence: low

Recommendations	Strength of Evidence and Recommendations
According to a third report, hypotonic ORS (total osmolarity <250 mmol/L) was recommended by WHO and several other advisory bodies as first-line therapy for mild to moderate dehydration resulting from diarrhea, arising from any cause. Recommendation: “Reduced ORS is recommended as the first-line therapy of mild to moderate dehydration in infants, children, and adults with acute diarrhea from any cause (strong, moderate), and in people with mild to moderate dehydration associated with vomiting or severe diarrhea." (p. e69) “Once the patient is rehydrated, maintenance fluids should be administered. Replace ongoing losses in stools from infants, children, and adults with ORS, until diarrhea and vomiting are resolved (strong, low)." (p. e70) Also, the guideline mentioned the following for mild to moderate dehydration (as adapted from Centers of Disease Control and Prevention). Rehydration therapy: For infants and children administer ORS, 50 mL/kg to 100 mL/kg over 3 to 4 hours. For adolescents and adults (≥30 kg) administer ORS, 2 L to 4 L After rehydration is complete, replacement of losses during maintenance: For body weight (<10 kg) administer 60 mL to 120 mL ORS for each diarrheal stool or vomiting episode, up to 500 mL/day. For body weight (>10 kg) administer 120 mL to 240 mL ORS for each diarrheal stool or vomiting episode, up to 1 L/day. For adolescents and adults administer ad libitum, up to 2 L/day. Continue replacement as above, as long as diarrhea and vomiting persists	Strength of recommendation: strong
Ondansetron Evidence: According to one article, studies have shown that in children, compared to placebo, with ondansetron more children had resolution of vomiting and there was reduction in the immediate need for hospitalization or intravenous rehydration. According to 3 studies, diarrhea was a side effect associated with ondansetron. Recommendation: “Antinausea and antiemetic (eg, ondansetron) may be given to facilitate tolerance of oral rehydration in children >4 years of age and in adolescents with acute gastroenteritis associated with vomiting (weak, moderate)." p. e71	**Ondansetron** For use of ondansetron Strength of evidence: moderate Strength of recommendation: weak

ESPGHAN = European society for pediatric gastroenterology; hepatology and infection; ESPID = European society for pediatric infectious diseases; GRADE = grading of recommendations assessment, development, and evaluation; IVT = intravenous therapy; kg = kilogram; L = liter; mg = milligram; mL = milliliter; mmol = millimole; ORS = oral rehydration solution; ORT = oral rehydration therapy; RCT = randomized controlled trial; WHO = world health organization.