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ORIGINAL ARTICLE

Recommendation document on rapid intravenous rehydration in acute gastroenteritis☆,☆☆

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Dehydration;
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Abstract
Introduction: The efficacy and safety of the Rapid Intravenous Rehydration (RIR) guidelines in children affected by dehydration secondary to acute gastroenteritis is supported by current scientific evidence, but there is also great variability in its use in clinical practice.
Objective: To prepare a document with evidence-based recommendations about RIR in paediatric population.
Methods: The project was developed based on GRADE methodology, according to the following work schedule: Working Group training; creation of a catalogue of questions about research and definition of ''relevant outcomes''; score and selection criteria for each item; bibliographic review; scientific evidence evaluation and synthesis (GRADE); review, discussion and creation of recommendations. 10 clinical questions and 15 relevant outcomes were created (7 about efficacy and 8 about security).

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☆☆ Previous presentation: This study was presented as a brief communication at the XXV Annual Meeting of the Sociedad Española de Urgencias Pediátricas, held online between March 3 and 6, 2021. It was awarded First Prize to the Best Brief Communication in this meeting.

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Results: 16 recommendations were set up, from which we can highlight as the main ones: 1) RIR is safe for children affected by mild-moderate dehydration secondary to acute gastroenteritis, unless expressly contraindicated or acute severe comorbidity (strong recommendation, moderate evidence). 2) Its use is recommended in this situation when oral rehydration has failed or due to contraindication (strong, high). 3) Isotonic fluids are recommended (strong, high), suggesting saline fluid as the first option (light, low), supplemented by glucose (2.5%) in those patients showing normoglycemia and ketosis (strong, moderate). 4) A rhythm of 20cc/kg/h is recommended (strong, high) during 1−4 h (strong, moderate).
Conclusions: This document establishes consensus recommendations, based on the available scientific evidence, which could contribute to the standardisation of the use of RIR in our setting.

PALABRAS CLAVE
Deshidratación;
Fluidoterapia;
Gastroenteritis;
Medicina basada en la evidencia

Documento de recomendaciones sobre la rehidratación intravenosa rápida en gastroenteritis aguda

Resumen
Introducción: Existe consenso en cuanto a la eficacia y seguridad de las pautas de rehidratación intravenosa rápida (RIR) en niños con deshidratación secundaria a gastroenteritis aguda (GEA), pero también una gran variabilidad en su uso en la práctica clínica.
Objetivo: elaborar un documento de recomendaciones sobre la RIR en población pediátrica basadas en la evidencia científica.
Metodología: Se diseñó un proyecto basado en metodología GRADE, siguiendo el siguiente esquema de trabajo: Formación del Grupo de Trabajo; formulación de preguntas de investigación y definición de ''desenlaces de interés''; puntuación y selección de ítems; revisión bibliográfica; evaluación y síntesis de la evidencia (GRADE); revisión, discusión y formulación de recomendaciones. Se incluyeron 10 preguntas clínicas y 15 desenlaces de interés (7 de eficacia y 8 de seguridad).
Resultados: Se establecieron 16 recomendaciones, destacando como principales: 1) La RIR es segura en niños con deshidratación leve-moderada secundaria a GEA, salvo contraindicación expresa o comorbilidad aguda grave *(recomendación fuerte, evidencia moderada)*; 2)Se recomienda su uso en este contexto cuando la rehidratación oral haya fracasado o esté contraindicada *(fuerte, alta);* 3)Se recomienda utilizar sueros isotónicos *(fuerte, alta)*, sugiriendo como primera opción el suero fisiológico *(débil, baja)*, añadiendo glucosa (2,5%) en pacientes con glucemia normal y cetosis *(fuerte, moderada)*. 4)Se recomienda un ritmo de infusión de 20 mL/kg/hora *(fuerte, alta)*, durante una a cuatro horas *(fuerte, moderada)*.
Conclusiones: En este documento se establecen recomendaciones de consenso, basadas en la evidencia científica disponible, que podrían contribuir a homogeneizar el uso de la RIR en nuestro medio.

Introduction

Dehydration (DH) is the most frequent complication developed by children with acute gastroenteritis (AGE); it causes significant morbidity and mortality and is associated with a substantial consumption of health care resources. Oral rehydration therapy (ORT) is the first-line treatment, but in cases of severe dehydration or in which ORT fails or is contraindicated, intravenous rehydration (IVR) is the main therapeutic alternative. Traditionally, IVR strategies followed the traditional method, based on slow replacement of the estimated fluid deficit[1] with hypotonic saline solutions. This approach requires complex calculations to establish fluid and electrolyte requirements, thus increasing risk of medication incidents and adverse events (AEs).[2]

Several decades ago, some authors started to question this approach and proposed new IVR regimens based on the rapid perfusion of generous amounts of isotonic solution to restore the extracellular fluid volume. These rapid intravenous rehydration (RIR) strategies improve renal perfusion (facilitating early correction of electrolyte imbalances and acid–base balance) and gastrointestinal perfusion (facilitating recovery of oral tolerance) and can shorten the necessary length of stay in the emergency department, which has eco-

nomic benefits.[1] Another advantage is that it requires simple calculations, reducing the risk of prescription errors.[3–5]

A substantial body of literature evinces that RIR is safe and effective[1] both in improving hydration status and reducing the frequency of admission of patients with dehydration secondary to AGE. However, caution should be exerted in the extrapolation of these conclusions to patients with profiles that have not been represented in these studies.

Although these rapid regimens are considered the standard for IVR in the international literature of the past year,[6,7] there is substantial heterogeneity as regards the optimal volume, rate and fluid composition used for rehydration. Some authors have questioned the administration of large volumes of isotonic fluid to correct dehydration, arguing that it could cause hyperchloraemic metabolic acidosis and suggested that balanced multielectrolyte solutions could be superior to normal saline solution (0.9% NS).[8,9] Some authors have also questioned the potential benefits of adding dextrose to the solutions used for RIR.[10]

In developing this document, the goal was to establish evidence-based recommendations for the use of RIR for treatment of dehydration in children with AGE, with the aim of standardising its use in paediatric emergency department (PEDs) nationwide.

Methods

We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop the document.[11,12] In the framework of the Working Group on Hydration and Electrolyte Disorders of the Sociedad Española de Urgencias Pediátricas (Spanish Society of Paediatric Emergency Care, SEUP), a working group (WG) was formed with 10 members and 2 coordinators. We formulated a series of research questions based on the P.I.C.O. model (population-intervention-comparison-outcome) and developed a list of ''outcomes of interest''. Subsequently, each member of the WG rated each research question and outcome of interest on a scale of 1–9, based on its relevance. To develop the document, the WG selected the items with a mean score of 4 or higher, and considered those with scores of 7 or greater key points for the development of the recommendations. The document included 10 clinical questions (Appendix B 1) and 15 outcomes of interest, including 7 related to efficacy and 8 related to safety (Appendix B 2).

We performed a literature search in the Medline, Embase, Cochrane Library, CINAHL, Web of Science, MEDES and LILACS using a list of keywords (Appendix B 3) and selecting studies conducted in the paediatric population in the past 10 years, published in English or Spanish, suing a stepwise mixed-methods search. In a first step, we reviewed clinical practice guidelines and systematic reviews and meta-analyses, and in a second step, we searched for original articles (clinical trials and observational studies).

Once the search was completed, we used the GRADE method to assess the quality of the available evidence to address each of the research questions. The GRADE method contemplates 4 levels of evidence (Table 1) based on the study design (randomised controlled trials: high quality, observational/descriptive studies: low quality) and certain modifying factors (Table 2). Whenever possible, each of the pre-established outcomes of interest were analysed individually before issuing an overall opinion on the set of outcomes analysed in each question.

For those questions for which it was an option, we summarised the results of the analysis in evidence profile tables. The rationale for the level of quality assigned to the evidence used in the analysis of each outcome of interest is given in the supplemental material of this article.

The results of the analysis of the available evidence were reviewed and debated to formulate the recommendations based on the criteria established by the GRADE approach (balance of benefits and harms, overall quality of the evidence for key outcomes, patient values and preferences, use of resources and costs) with the consensus of a minimum of 80% of the members of the WG. The recommendations were classified based on the direction (in favour/against), the strength (strong/weak) and the level of quality of the evidence supporting the recommendation.

Lastly, the document was revised and endorsed by the Scientific Committee of the SEUP.

Results

Appendix B 4 summarises the main studies reviewed. A more detailed commentary of the literature review and evidence used to address each of the questions is available in the supplemental material (Appendix B 5). Some of the limitations that we ought to mention in relation to the interpretation of the conclusions of the reviewed literature included the scarcity of studies conducted in Europe, where the population and health care systems are more similar to those in Spain, and the inclusion criteria applied in many studies, which limited the evidence available in children aged more than 12 years or with body weights greater than 33 kg.

We did not find any studies documenting the preferences of patients or caregivers in relation to RIR. In consequence, the WG could not consider these aspects in the development of the recommendations. When it came to the assessment of costs, several studies provide evidence that the use of RIR achieves a reduction in the frequency of hospital admission and the length of stay in the emergency department, which has clinical benefits and is also a sign of improved efficiency.[13] When evidence was very weak or non-existent, recommendations were developed based on expert opinion.

The final recommendations were approved by every member of the WG. They are presented in Table 3.

Question 1: In which patients is RIR Indicated?

Question 2: In which patients is RIR contraindicated?

We did not find any publication in which the primary or secondary objective was to establish the indications and/or contraindications for RIR. Given the absence of direct evidence, we formulated recommendations by consensus based on the extrapolation of the inclusion and exclusion criteria applied in different studies.[14–24] We took into account the risk-benefit balance, as it was not possible to establish the safety or efficacy of these strategies in patient profiles that, due to age, the underlying disease or particular circumstances, were not represented in the published evidence.

Table 1 Classification of the quality of evidence based on the GRADE method.

Quality	Definition
High	Further research is unlikely to change our confidence in the estimated effect of the intervention
Moderate	Our confidence in the effects and magnitude of the intervention may change with future research
Low	Further research is very likely to change our confidence in the estimated effect and magnitude of the intervention
Very low	Any estimate of effect is uncertain

Table 2 Modifiers of the quality of evidence based on the GRADE method.

Type of study	Initial quality of evidence	Reduces quality of evidence	Increases quality of evidence	Final quality of evidence
Randomised trial	High ++++	**Risk of bias** −1: Serious −2: Very serious		High ++++
		Inconsistency −1: Serious −2: Very serious	**Large effect** +1: Large +2: Very large	Moderate +++
Observational studies	Low ++	**Indirectness** −1: Serious −2: Very serious	**Dose-response gradient** +1: Evidence of gradient	Low ++
		Imprecision −1: Serious −2: Very serious	**Residual confusion** +1	Very low +
		Publication bias −1: Serious −2: Very serious		

Given the heterogeneity of the age criteria applied in different studies, we establish the recommendation of using RIR strategies from age 3 months.

Patients with severe dehydration may exhibit signs of shock and require stabilization. Although this is not an absolute contraindication, we decided to exclude severe dehydration from the general indications of RIR, and we consider personalised management in these patients the prudent approach.

The presence of an acute comorbidity or suspected surgical disease are not considered absolute contraindications. However, the objective of this document was to establish specific recommendations for RIR for management of dehydration secondary to AGE. In other clinical contexts, dehydration must be corrected taking into account its pathophysiology, severity and relevant laboratory parameters. Adhering to the principle of prudence, and in agreement with other authors,[7,15,16,22] we decided to consider severe abnormalities in sodium levels (<130 mEq/L or >150 mEq/L) as a relative contraindication, recommending a personalised rehydration strategy in these cases.

Question 3: Is it necessary to perform laboratory tests before initiation of RIR?

There is no direct evidence based on which to establish recommendations on the subject. There is no evidence in the current literature supporting routine performance of blood tests in patients with AGE. However, it seems prudent to recommend measurement of certain plasma levels in select patients, including those to receive intravenous rehydration, as recommended in previous guidelines.[25,26]

We identified several works that sought to determine the usefulness of different laboratory parameters to assess the severity of dehydration, guide the prescription and/or adjustment of rehydration regimens and predict the need of hospital admission. Their results were contradictory and, therefore, the quality of the available evidence is low. However, some authors noted that some laboratory parameters (bicarbonate, sodium, urea and creatinine) could contribute to the assessment of the severity of dehydration[27–31] and help identify patients that could be managed in short-stay units,[32] which would streamline care delivery and avoid costs associated with longer hospitalizations.

On the other hand, the WG considered severe disorders of plasma sodium (<130 mEq/L o >150 mEq/L) a relative contraindication for RIR, so measurement of serum sodium levels would be necessary to individualise the rehydration strategy in the case of severe hypernatraemia or hyponatraemia.

As regards plasma ketone levels, the evidence on the usefulness of this marker for assessment of the degree of dehydration in children with AGE is scant.[30] Nevertheless, the WG considered ketone levels a useful parameter to determine the optimal composition of the rehydration solution, so we recommend determination of ketone levels if the test is available.

Table 3 Summary of recommendations.

Question	Recommendation	Strength of recommendation	Quality of evidence
In which patients is RIR indicated?	We recommend prescribing RIR in children with mild to moderate dehydration secondary to AGE in whom oral rehydration is contraindicated or has failed	Strong	High
In which patients is RIR contraindicated?	For the Spanish population, we do not recommend use of RIR in infants aged less than 3 months or in patients with haemodynamic instability, severe electrolyte imbalances (sodium, <130 mmol/L or >150 mmol/L) or systemic disease affecting haemodynamic homeostasis and/or fluid and electrolyte balance	Strong	Not available
Is it necessary to perform laboratory tests before initiation of RIR?	We recommend performance of blood tests (including venous blood gas analysis, and electrolyte, glucose, urea and creatinine levels) in every paediatric patient in whom venous access is established for delivery of intravenous rehydration	Strong	Low
	We recommend measurement of plasma ketone levels	Weak	Low
Which clinical assessments should be done during RIR?	We recommend the following assessments during rapid intravenous rehydration: ● **Vital signs monitoring:** heart rate and blood pressure (at least in the initial assessment) ● **Physical examination:** general health, level of dehydration (we recommend use of validated scales) and symptoms and signs of volume overload ● **Fluid balance** (input and output) The frequency with which these assessments should be performed depends on the clinical condition and evolution of the patient	Strong	Low
Are any diagnostic tests required for follow-up after completion of RIR?	We recommend repeated blood testing (electrolytes, glucose, urea, creatinine, venous blood gas analysis) in patients with clinically significant abnormalities in the baseline workup or with unfavourable outcomes	Strong	Low
What is the appropriate flow rate for RIR?	We recommend administration of RIR at a rate of 20 mL/kg/h	Strong	High
	We suggest a maximum flow rate of 700 mL/h	Weak	Not available
What is the appropriate duration of RIR?	We recommend maintenance of RIR for 1–4 h, depending on the estimated fluid losses and the clinical response of the patient	Strong	Moderate
What type of solution should be used for RIR?	We recommend the use of isotonic solutions for RIR	Strong	High
	We recommend physiological saline (0.9% NS) as the first choice, with lactated Ringer or Plasma-Lyte A as possible alternatives	Weak	Low
Should dextrose be added to the solution used for RIR?	We recommend using isotonic saline with 2.5% dextrose in patients with normal blood glucose levels and ketosis	Strong	Moderate
	In patients with normal serum glucose and ketone levels, we recommend using isotonic saline with 2.5% dextrose	Weak	Low
	In patients with normal glucose levels in whom serum ketone levels are not known, we suggest using isotonic saline with 2.5% dextrose	Weak	Low
	In patients with hyperglycaemia (glucose >140 mg/dL), we recommend using isotonic saline WITHOUT dextrose	Strong	Low
Is rapid intravenous rehydration safe?	RIR is safe in patients with DH secondary to AGE in whom oral rehydration is contraindicated or has failed, unless there is a direct contraindication or severe acute comorbidity	Strong	High

AGE, acute gastroenteritis; DH, dehydration; RIR, rapid intravenous rehydration.

Question 4: Which clinical assessments should be done during RIR?

Question 5: Are any diagnostic tests required for follow-up after completion of RIR?. There is no direct evidence on which to base recommendations regarding clinical assessments and laboratory tests for patient monitoring during RIR and for follow-up after RIR. However, the reviewed studies included clinical assessments and laboratory tests in the methodology, either to assess the response to treatment and/or to monitor for potential AEs. The WG developed recommendations by consensus based on the extrapolation of the tests and assessments performed in reviewed studies and their reported usefulness in guiding decision-making and adjustments to treatment.

Research purposes aside, measuring body weight after rehydration appears to be of little use in the paediatric emergency care setting.

To monitor the clinical condition of the patient and guide treatment, we recommend period re-evaluation of the severity of dehydration by means of validated scales (Gorelick scale[9,16,22]; Clinical Dehydration Scale[6]), watch for signs of volume overload or other AEs[6,7,9,14,16,18,20,22,30] and measure the balance of fluid inputs and outputs [7,14,17,19,20,26] with ongoing replacement of fluid deficits.

Given the frequency with which abnormal levels of biochemical markers are reported in post-rehydration testing in the reviewed literature, we do not believe that routine testing is warranted. However, the WG considers prudent to perform follow-up tests in patients that exhibited significant abnormalities in the baseline tests or with unfavourable outcomes.

Question 6: What is the appropriate flow rate for RIR?

Question 7: What is the appropriate duration of RIR?. Table 4 summarises the evidence available to answer these questions. A summary of the analysis performed to determine the quality of the evidence based on the GRADE criteria is available in Appendix B 6.

So-called ''ultrarapid'' strategies (rates of infusion >20 mL/kg/h) have not proven superior to standard RIR,[6,33,34] and there are even studies[6] suggesting poorer outcomes with ultrarapid rehydration (higher rate of admission and persistence of metabolic acidosis. Thus, we found no evidence to justify the use of this approach, and the WG, in agreement with the guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)[25] recommends a flow rate of 20 mL/kg/h. Due to the lack of evidence, we established a maximum rate of 700 mL/h based on real-world clinical practice, the RIR protocols used by the members of the WG and the maximum flow rates used in studies conducted in Spain, which exclude patients with weights under 35 kg.

Other than the duration established by the ESPGHAN,[25] we did not find any direct evidence to provide recommendations regarding the duration of RIR. It is essential to make accurate estimates of the level of dehydration and perform clinical assessments at regular intervals to adjust the total volume of fluids required to replace fluid losses. Considering that the recommendations in this document are meant for patients with mild to moderate dehydration and an estimated fluid deficit of 3%–9% (equivalent to 30—90 mL/kg), we would suggest delivery of RIR for 1–4 h (total delivered volume, 20—80 mL/kg) based on the degree of dehydration and the clinical evolution of the patient.

Question 8: What type of solution should be used for RIR?

Table 5 summarises the analysis of the available evidence used to answer these questions. A summary of the analysis performed to determine the quality of the evidence based on the GRADE criteria is available in Appendix B 7.

The current evidence demonstrates that IVR with isotonic saline in children with AGE is safe, effective[5,35,36] and superior to rehydration with hypotonic solution as regards prevention of iatrogenic euvolemic hyponatraemia, intravascular volume expansion and early correction of volume deficits.[8,9] However, the evidence is insufficient to determine which is the optimal type of isotonic fluid.

Reviewed studies[35,36] recommend rehydration with isotonic fluids, and 0.9% NS and lactated Ringer solution (LR) are both widely accepted options. In Europe and the United States, 0.9% NS is the most commonly used crystalloid solution. Some authors propose that the use of balanced solutions such as LR or Plasma-Lyte (PLA) could prevent potential AEs derived from the infusion of substantial volumes of 0.9% NS, chiefly hypernatraemia and hyperchloraemic metabolic acidosis. Some studies[9,17] found differences in the evolution of specific chemistry markers (bicarbonate and chloride) in support of the use of balanced solutions, however, these differences were of little clinical relevance and were not associated with the proportion of hospital admission, the duration of rehydration or the total volume of fluids administered.

Only the study by Kartha et al.[14] made any type of economic analysis, considering only the cost of the saline used for RIR, which would support the use of 0.9% NS versus LR.

Since 0.9% NS is the solution used most extensively in Spain and there is no current evidence of the superiority of other crystalloids, we recommend use of 0.9% NS as the first-line option. Balanced solutions are a reasonable alternative.

Question 9: Should dextrose be added to the solution used for RIR?

Table 6 details the analysis performed to answer these questions. A summary of the analysis performed to determine the quality of the evidence based on the GRADE criteria is available in Appendix B 8.

Children with dehydration secondary to AGE frequently present with accumulation of ketone bodies secondary to the metabolism of free fatty acids in the context of an insufficient carbohydrate intake. This state of ketosis may contribute to the loss of oral tolerance.[21,37] Some authors[38,39] theorise that administration of dextrose in the rehydration solution could contribute to early improvement of blood ketone levels, thus facilitating recovery of oral tolerance and outpatient management of these patients.

Based on the reviewed literature, RIR with isotonic saline and dextrose is not superior to use of isotonic saline alone, except in the reduction of blood ketone levels, whose clinical relevance has not been clearly established beyond pathophysiological hypotheses. Although the quality of the available evidence is limited, the results of previous studies suggests that use of isotonic saline solutions with dextrose

Table 4 What is the appropriate rate of infusion for RIR? When should RIR be discontinued? Summary of outcomes of interest and quality of the evidence.

Outcome	Study, year of publication	Results		Quality of evidence (Appendix 6)
Success of rehydration	Nager, 2010	**Input/output balance. Ultrarapid** vs. **standard RIR** Emesis volume: 69 vs 21 mL/h. Urine output. 93 vs 24 mL/h. Stool output: 45 vs 25 mL/h	*P* .042	Moderate
		Post-RH weight gain: Ultrarapid, 474 g (4.2%) vs standard RIR, 408 g (3.8%)	*P* .343	
		Change in HR (initial-final): Ultrarapid, 147−122 bpm vs standard RIR 154−123 bpm	*P* .163	
	Freedman, 2011	**Resolution of DH at 2 h:** Ultrarapid: 41/114 (36%) vs standard: 33/112 (29%) Absolute difference, 6.5% (95% CI, −5.7% to +18.7%)	*P* .32	
		Need of prolonged treatment [¥] Ultrarapid: 59/114 (52%) vs standard: 48/112 (43%)	*P* .18	
	Azarfar, 2014	**Resolution of vomiting at 4 h:** Intervention group: 63/75 (84%) vs control group: 62/75 (82%)	*P* > .05	
	Houston, 2019	**Time to correction of DH:** No differences between groups	*P* .9	
Recovery of oral tolerance	Freedman, 2011	**Tolerance of 5 mL/kg at 2 h:** Ultrarapid: 29/114 (25%) vs standard RIR: 36/112 (32%)	*P* .31	Moderate
	Houston, 2019	**Time to recovery of oral tolerance:** Plan C: 6.5 h (2.2−36.3)[⊤] vs ''Slow'' group 11.9 h (1.0−30.6)[⊤]	*P* .27	
Admission	Nager, 2010	Ultrarapid: 1/46 vs standard RIR: 3/46		Moderate
	Freedman, 2011	Ultrarapid: 33/114 (29%) vs standard RIR: 19/112 (17%)	*P* .04	
	Iro, 2018	No differences. n = 468. RR 1.30 (95% CI, 0.87−1.93)		
Return visit	Nager, 2010	Ultrarapid: 7/45 (15.6%; 95% CI, 6.5%−29.5%) vs standard RIR: 6/43 (14%; 95% CI, 5.3%−28%)	*P* .999	Moderate
	Freedman, 2011	**In the first 72 h:** Ultrarapid: 16/114 (14%) vs standard RIR: 13/111 (12%)	*P* .69	
	Iro, 2018	No differences: n = 439. RR 1.39 (95% CI, 0.68−2.85)		
	Houston, 2019	No return visit within 7 days in any group		
Length of stay	Freedman, 2011	**Time to discharge from emergency department:** Ultrarapid: 6.3 h vs standard RIR: 5 h	*P* .03	Low
	Houston, 2019	No differences between groups	*P* .8	
Changes in bicarbonate (HCO_3)	Freedman, 2011	**Change in bicarbonate (final-initial) at 4 h:** Ultrarapid: −0.31 mmol/L (2.2)* vs standard: +0.56 mmol/L (1.9)*	*P* .01	Low
pH	Freedman, 2011	**Mean pH at 4 h:** Ultrarapid: 7.34 (0.04)* vs standard RIR: 7.35 (0.04)*	*P* .10	Low
Changes in sodium (Na^+)	Nager, 2010	**Final sodium levels:** Ultrarapid 141 mmol/L (3.7)* vs standard RIR 142 mmol/L (3.9)*	*P* > .05	Moderate
	Freedman, 2011	**Sodium levels at 4 h:** Ultrarapid: 138 mmol/L (2.0)* vs standard RIR: 137.5 mmol/L (2.0)*	*P* .06	
	Houston, 2019	**Sodium levels at 8 h:** Plan C: 142 mmol/L (135−147)[⊤] vs ''slow'' group: 142 mmol/L (138−148)[⊤]	*P* .32	
		Dysnatraemia (Na^+ < 135 or >145 mmol/L) at 8 h: Plan C: 29/50 (58%) vs ''slow'' group: 25/52 (48%)		
Changes in potassium (K^+)	Nager, 2010	**Final potassium levels:** Ultrarapid 4.0 mmol/L (0.6)* vs standard RIR 4.1 mmol/L (0.6)*	*P* > .05	Moderate
	Freedman, 2011	**Potassium levels at 4 h:** Ultrarapid: 3.8 mmol/L (0.5)* vs standard RIR: 3.9 mmol/L (0.5)*	*P* .01	
Changes in glucose	Nager, 2010	**Final glucose levels:** Ultrarapid 79 mg/dL (18.1)* vs standard RIR 79 mg/dL (12.6)*	*P* > .05	High
	Freedman, 2011	**Glucose levels at 4 h:** Ultrarapid: 97.29 mg/dL (28.83)* vs standard RIR: 93.68 mg/dL (21.62)*	*P* .20	

WHO plan C:
Phase 1: 30 mL/kg over 30 min if age > 1 year (or over 1 h if age < 1 year). In the case of shock, boluses of 0.9% NS at 20 mL/kg as quickly as possible (to a maximum of 3 boluses).
Phase 2: 70 mL/kg over 2.5 h if age > 1 year (or over 5 h if age < 1 year).
DH, dehydration; HR, heart rate; RH, rehydration; RIR, rapid intravenous rehydration; 0.9% NS, isotonic saline.
* Values expressed as mean (SD).
⊤ Values expressed as median (IQR).
¥ Need of prolonged treatment: composite outcome defined as any of the following: admission in initial emergency visit, stay longer than 6 h after initiation of intravenous treatment or re-evaluation leading to admission within 72 h of treatment initiation.

Table 5 Question: What type of solution should be used for RIR? Summary of outcomes of interest and quality of evidence.

Outcome	Study, year of publication	Results		Quality of evidence (Appendix 7)
Success of rehydration	Mahajan, 2012	**Change in pH baseline-post-rehydration***: 0.9% NS: 7.09 (0.11) to 7.21 (0.09) vs LR: 7.17 (0.11) to 7.28 (0.09)	*P* .17	Moderate
		Dose of IV and oral fluids†**** : 0.9% NS 530 mL/kg (324–750) vs LR 310 mL/kg (230–365)	*P* .01	
	Kartha, 2017	**Resolution of signs of severe DH after treatment (6 h)**: 0.9% NS 94% vs LR 97%	*P* > .05	
	Allen, 2016	**Dose of fluids**: 0.9% NS 38.4 mL/kg vs PLA 39.6 mL/kg	*P* > .05	
		Assessment of DH severity at (Gorelick) at 2 and 4 h*: 0.9% NS (baseline/2/4 h):5.3 (1.11)/ 2.8 (1.74)/ 1.41 (1.08) vs PLA (baseline/2/4 h): 5.2 (0.93)/ 2 (1.45)/ 2 (1.45) Improvement in hydration status (Gorelick) at 2 h in PLA vs 0.9% NS group. No differences at 4 h	*P* .03	
		Time to rehydration (hours): 0.9% NS 7.0 (2.7) vs PLA 6.1 (1.75)	*P* .13	
Hospital admission	Allen, 2016	0.9% NS 29% vs PLA 31%	*P* .86	Low
Length of stay/time to dehydration	Majahan, 2012	**Length of stay (hours)***: 0.9% NS 51 h (36–71) vs LR 38 h (27–50)	*P* .03	Low
	Kartha, 2017	**Length of stay (days)**†**** : 0.9% NS 2.0 (2.0–2.0) vs LR 2.0 (1.0–2.0)	*P* .125	
Changes in bicarbonate (HCO_3)	Mahajan, 2012	**Change in HCO_3, baseline to post-RIR***: 0.9% NS: 8.6 (2.8) to 9.3 (2.6) mmol/L vs LR: 9.4 (2.7) to 13.4 (2.1) mmol/L	*P* .02	Moderate
	Kartha, 2017	**HCO_3 levels at 6 h**†**** : 0.9% NS: 16 mmol/L (12–18) vs LR: 16 mmol/L (13–18)	*P* .659	
	Allen, 2016	**HCO_3 at baseline and at 4 h***: 0.9% NS: 17.8 (3.82) to 18.0 (3.67) mmol/L vs PLA: 16.9 (3.51) to 18.5 (3.74) mmol/L	*P* .004	
pH	Mahajan, 2012	**Change in pH, baseline to post-RIR***: 0.9% NS: 7.09 (0.11) to 7.21 (0.09) vs LR: 7.17 (0.11) to 7.28 (0.09)	*P* .17	Moderate
	Kartha, 2017	**Correction of pH > 7.35:** 0.9% NS 23% vs LR 38%	*P* .189	
Changes in sodium (Na^+)	Mahajan, 2012	**Change in Na^+, baseline to post-RIR***: 0.9% NS: 132.8 (6.2) to 131 (9.3) mmol/L vs LR: 138.7 (6) to 135.0 (3.3) mmol/L	*P* .05	Moderate
	Kartha, 2017	**Na^+ levels at 6 h**†**** : 0.9% NS: 138 mmol/L (135–141) vs LR: 138 mmol/L (136–140)	*P* .518	
	Allen, 2016	One patient in each group developed mild hyponatraemia (Na^+ 131–135 mmol/L) after 4 h of treatment		
Changes in potassium (K^+)	Mahajan, 2012	**Change in K^+, baseline to post-RIR***: 0.9% NS: 4.5 ± 0.9–3.6 ± 0.9 mmol/L vs LR: 4.6 ± 0.9–3.9 ± 0.6 mmol/L	*P* .03	Low
	Kartha, 2017	**K^+ at 6 h**†**** : 0.9% NS: 4 mmol/L (3.6–4.3) vs LR: 4.1 mmol/L (3.9–4.2)	*P* .273	
	Allen, 2016	8 patients developed hypokalaemia (K < 3 mmol/L) at 4 h of treatment (6/38 0.9% NS vs 2/39 PLA) 4 patients developed hyperkalaemia (>5.6 mmol/L) (3/38 in 0.9% NS vs 1/39 in PLA) attributed to haemolysis by the authors		
Changes in chloride (Cl−)	Mahajan, 2012	**Change in Cl−, baseline to post-RIR** *: 0.9% NS: 100.8 (1.0) to 101 (1.4) vs LR: 101.4 (1.1) to 101.8 (1.6)	*P* .274	Moderate
	Kartha, 2017	**Cl− levels at 6 h**†**** : 0.9% NS: 110 mmol/L (102–113) vs LR: 108 mmol/L (104–111)	*P* .654	
	Allen, 2016	**Change in Cl−, baseline-4 h***: 0.9% NS: 103.5 (4.2) to 108.5 (4.9) mmol/L vs PLA: 103.0 (4.7) to 104.5 (3.2) mmol/L	*P* < .001	

DH, dehydration; IV, intravenous; LR, lactated ringer solution; PLA, Plasma-Lyte A; RIR, rapid intravenous rehydration; 0.9% NS, isotonic (normal) saline solution.

* Values expressed as mean (SD).

† Values expressed as median (IQR).

Table 6 Question: Should dextrose be added to rehydration saline? Summary of outcomes of interest and quality of evidence.

Outcome	Study, year of publication	Results		Quality of evidence (Appendix 8)
Success of rehydration (improvement in hydration status)	Levy, 2013	**Change in general appearance score at 3 h**[T] : 0.9% NS 1(0—1) vs D5NS 1(0—1)	Did not provide statistical analysis	Moderate
	Sendarrubias, 2017	**Change in Gorelick scale at 2 h:** 0.9% NS −2 vs D2.5NS −2	*P* .41	
	Janet, 2015	**Change in Gorelick scale at 4 h**[T] : Baseline: 3 (2—4) vs at 4 h: 0 (0—1)	*P* < .001	
Recovery of oral tolerance	Levy, 2013	0.9% NS 75% vs D5NS 76%	Did not provide statistical analysis	Low
Admission	Grigsby, 2019	0.9% NS 65/163 (40.5%) vs DNS 56/170 (32.9%)	RR 0.83 (95% CI, 0.62–1.10)	Low
	Levy, 2013	0.9% NS 41/94 (44%) vs D5NS 33/94 (35%)	9% difference (95% CI, −5 to +22%)	
		Subgroup with HCO_3 < 20 mmol/L (n = 123) vs 0.9% NS 53% vs D5NS 46%	7% difference (95% CI, −10 to +25%)	
	Sendarrubias, 2017	0.9% NS 24/69 (34.8%) vs D2.5NS 23/76 (30.3%)	*P* .59	
	Janet, 2015	D2.5NS 14/83 (16.8%)		
Return visit	Grigsby, 2019	0.9% NS 21/99 (21.2%) vs DNS 11/102 (10.8%)	RR 0.54 (95% CI, 0.24–1.22)	Very low
	Levy, 2013	0.9% NS 13/54 (24%) vs D5NS 8/46 (17%)	7% difference (95% CI, −9 to +23%)	
		Subgroup with HCO_3 <20 mmol/L (n = 55): 0.9% NS 30% vs D5NS 11%	19% difference (95% CI, −2 to +40%)	
	Sendarrubias, 2017	0.9% NS 8/45 (17.8%) vs D2.5NS 3/53 (5.6%). Risk difference 12.2% (95% CI, —0.7–24.9)	*P* .091	
	Janet, 2015	D2.5NS 5/69 (7.2%)		
Outcome	Study, year of publication	Results		Quality of evidence (Appendix 8)
Length of stay in emergency department	Levy, 2013	0.9% NS 280 min (246—361)[T] vs D5NS 288 min (238—349)[T]	Did not provide statistical analysis	Low
Reduction in ketone levels	Levy, 2013	At 1 h: 0.9% NS −0.1 mmol/L vs D5NS −1.2 mmol/L	Mean difference 1.1 mmol/L (95% CI, 0.4–1.9 mmol/L)	Moderate
		At 2 h: 0.9% NS −0.3 mmol/L vs DNS 5% −1.9 mmol/L	Mean difference 1.6 mmol/L (95% CI, 0.9–2.3 mmol/L)	
	Sendarrubias, 2017	At 2 h: 0.9% NS + 0.4 mmol/L vs D2.5NS −1.1 mmol/L	*P* < .001	
		At 4 h: 0.9% NS + 0.18 mmol/L vs DNS 2.5% −0.28 mmol/L	*P* .088	
	Janet, 2015	Baseline: 1.5 mmol/L (0.6—4.0)[T] vs at 4 h: 0.8 mmol/L (0.2—2.8)[T]	*P* .001	
Hipoglucemia	Levy, 2013	Pre-RIR: 26 with hypoglycaemia (<60 mg/dL) **At 1 h:**	Low	

(*Continued*)

Outcome	Study, year of publication	Results		Quality of evidence (Appendix 8)
		D5NS: normalization of glucose in 100% of hypoglycaemic patients 0.9% NS: hypoglycaemia persisted in 100% of patients with hypoglycaemia at baseline + 12 patients with normal glucose at baseline with newly developed hypoglycaemia **At 2 h:** D5NS: 3 patients with hypoglycaemia 0.9% NS: 3 patients with hypoglycaemia		
	Sendarrubias, 2017	No cases of hypoglycaemia reported. However, there were differences in the blood glucose trends: **At 2 h:** 0.9% NS −17 mg/dL vs D2.5NS +30 mg/dL **At 4 h**: 0.9% NS −8.6 mg/dL vs D2.5NS +0.96 mg/dL	Comparison at 2 h: $P < .001$ Comparison at 4 h: P .074	
Hiperglucemia	Levy, 2013	Levy et al did NOT report cases of hyperglycaemia. However, there were differences in blood glucose trends[Ŧ] **At 1 h**: D5NS 272 mg/dL (221−361) vs 0.9% NS 70 mg/dL (57−86)[Ŧ] **At 2 h:** D5NS 154 mg/dL (121−221) vs 0.9% NS 106 mg/dL (87−172)[Ŧ]	Did not provide statistical analysis	Low
	Sendarrubias, 2017	Hyperglycaemia (>200 mg/dL): 0.9% NS 0/69 vs D2.5NS 4/76 (5.3%)	Statistical analysis data nor reported	
	Janet, 2015	Did not report cases of hyperglycaemia. Changes in blood glucose: Baseline 91.9 mg/dL (95% CI, 85.4−98.4) vs at 4 h 102 mg/dL (95% CI, 94.0−110.8)	P .020	

D5NS, 5% dextrose in normal saline; D2.5NS, 2.5% dextrose in normal saline; DNS, dextrose normal saline; RIR, rapid intravenous rehydration; 0.9% NS, isotonic (normal) saline solution.
*Values expressed as mean (SD).
Ŧ Values expressed as median (IQR).

Table 7 Question: Are RIR strategies safe? Summary of outcomes of interest and quality of the evidence.

Outcome	Study, year of publication	Results	Quality of evidence (Appendix 9)
Mortality	Houston, 2019	Overall mortality: 4/ 122 (3.3%) **Plan C group:** 2 *(1 patient with heart failure, only death attributable to the intervention based on the authors)* **Slow rehydration group:** 2	High
	Mahajan, 2012	Overall mortality: 1/22 (4.5%) **LR group:** 0 0.9% **NS group:** 1	
	Rest of studies	No deaths reported	
Severe adverse events	Houston, 2019	At 48 h: **Plan C group: 3 (5%)** *1 heart failure (only one attributable to intervention according to authors)*[¥] 1 AGE + pneumonia with positive blood culture (*H. influenzae*)[¥] 1 status epilepticus with favourable outcome **Slow rehydration group: 2 (3%)*** 1 AGE + pneumonia with right-sided pleural effusion → progressive difficulty breathing[¥] 1 critically ill patient with hypoxaemia at admission (seizures, respiratory arrest → cardiac arrest)[¥] *The authors reported another severe AE in this group (seizures in the slow rehydration group at 101 h of random allocation, with a favourable outcome)	High
	Rest of studies	Not reported	
Non-severe adverse events	Freedman, 2011	**Peripheral oedema:** 6 cases (2.7%) Ultrafast group (2 cases) vs standard RIR group (4 cases) **Interstitial displacement of peripheral catheter:** 2 cases (0.9%) Ultrafast group, 1 vs standard RIR group, 1	Very low
	Freedman, 2013 (same sample as Freedman 2011)	Volume overload: 9 possible cases → **None** considered clinically relevant by the physician in charge	
	Rest of studies	None reported	

WHO plan C:
Phase 1: 30 mL/kg over 30 min if age > 1 year (or over 1 h if age < 1 year). In the case of shock, boluses of 0.9% NS at 20 mL/kg as quickly as possible (to a maximum of 3 boluses).
Phase 2: 70 mL/kg over 2.5 h if age > 1 year (or over 5 h if age < 1 year).
AE, adverse event; AGE, acute gastroenteritis; BC, blood culture; LR, lactated Ringer solution; RIR, rapid intravenous rehydration; 0.9% NS, physiological saline solution.
[¥] Death.

allow normalization of blood glucose levels in patients with hypoglycaemia at baseline without causing clinically relevant hyperglycaemia.

However, as Grigsby et al. noted,[10] due to the limited quality of the available evidence, it is also not possible to exclude that the addition of dextrose to isotonic saline solution for RIR could offer significant clinical benefits. Along the same lines, Niescierenko et al.[37] considered that the outcomes reported by Levy et al.[21] and Sendarrubias et al.,[16] with a reduction in the proportion of patients requiring admission and a significant decrease in the number of unscheduled return visits in patients rehydrated with isotonic saline with dextrose, could have clinical and economic implications that need to be taken into account when establishing recommendations.

To assess real-world clinical practices in Spain, beyond the personal experience of the members of the WG, we reviewed the results of a survey that explored the implementation and variations of RIR protocols in PEDs in Spain.[40] Of the 87 facilities that participated, 53% used isotonic saline with dextrose in their RIR protocols, with glucose used most frequently at a concentration of 2.5% (42%).

At present, there is no 2.5% dextrose normal saline solution commercially distributed by the pharmaceutical

industry. Considering this limitation, the best option would be its preparation by hospital pharmacies. If this is not possible, the alternative is to establish a protocol for its preparation by the nursing staff of the unit.

Question 10: Is rapid intravenous rehydration safe?

Table 7 summarises the analysis of the available evidence used to answer these questions. A summary of the analysis performed to determine the quality of the evidence based on the GRADE criteria is available in Appendix B 9.

In this section, we reviewed the available evidence on mortality and AEs (severe/non-severe) defined in this document as outcomes of interest.[41]

The main limitations in addressing this question concerned the methodological heterogeneity of published studies and the fact that the methods section of most of the studies that we reviewed[6,7,9,10,14,15,17–21,24,33,34] did not include an explicit definition of the AEs that should be monitored and recorded.

Despite the heterogeneity of the reviewed literature as regards the population under study (inclusion and exclusion criteria), the intervention (composition of the solution, rate of infusion and total volume of rehydration) and the outcome variables, we consider that there was evidence of sufficient quality to assert that RIR is a safe rehydration strategy for patients with dehydration secondary to AGE in Spain, as long as there is not a direct contraindication or a severe acute comorbidity (Table 3).

Conclusion

This position statement on the use of RIR was developed based on the available scientific evidence and applying the GRADE approach, and subsequently endorsed by the Scientific Committee of the SEUP. It addresses 10 clinical questions and formulates 16 recommendations regarding the safety of RIR, its indications and contraindications, its duration, the optimal composition of the administered solution, the rate of infusion and the clinical assessments and tests to be performed. These recommendations could contribute to the nationwide standardization of the use of RIR in the paediatric emergency care setting in Spain.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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