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ORIGINAL ARTICLE

# Efficacy of racecadotril vs. smectite, probiotics or zinc as an integral part of treatment of acute diarrhea in children under five years: A meta-analysis of multiple treatments

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## Abstract

**Rationale:** *Despite major advances in treatment, acute diarrhea continues to be a public health problem in children under five years. There is no systematic approach to treatment and most evidence is assembled comparing active treatment vs. placebo.* **Objective:** *Systematic review of evidence on efficacy of adjuvants for treatment of acute diarrhea through a network meta-analysis.* **Methods:** *A systematic search of multiple databases searching clinical trials related to the use of racecadotril, smectite, Lactobacillus GG, Lactobacillus reuteri, Saccharomyces boulardii and zinc as adjuvants in acute diarrhea was done. The primary endpoint was duration of diarrhea. Information is displayed through network meta-analysis. The superiority of each coadjutant was analyzed by Sucra approach.* **Results:** *Network meta-analysis showed racecadotril was better when compared with placebo and other adjuvants. Sucra analysis showed racecadotril as the first option followed by smectite and Lactobacillus reuteri.* **Interpretation:** *Considering a strategic decision making approach, network meta-analysis allows us to establish the therapeutic superiority of racecadotril as an adjunct for the comprehensive management of acute diarrhea in children aged less than five years.* (Gac Med Mex. 2015;151:306-14)

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## Introduction

Despite major advances over the past few decades in the use of efficient oral hydration regimens, acute diarrheal disease in children younger than 5 years continues to represent a relevant health problem that generates significant morbidity and an important burden imposed on society[1]. Currently, it is considered to be responsible for 10% of all deaths in children < 5 years of age, which in absolute numbers represents around 800,000 deaths every year and 240,000

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visits to the emergency department/country/year[2,3]. It generates hospitalization rates of 1 in every 25 children < 5 years of age with acute diarrhea[4] and produces USD 11,465,541 in direct costs for each 100,000 sick children; it is estimated to produce over 2 trillion dollar expenses for outpatient or hospital management[5,6].

Despite the ubiquity of the disease, and the amount and diversity of publications on the subject, there are significant variations in the world on the type of treatments established for this type of children[7]. Recently, a survey on prescription patterns by emergency pediatricians in the USA[8] and an analysis of practice patterns in Canada[9] documented significant variations in therapeutic approaches, many of them due to inconsistent implementation of existing clinical practice guidelines (CPG) or medical directives. This way, only 28% of emergency physicians were identified to efficiently manage a CPG/care pathway and only in 38% of the cases were there written and validated directives on oral hydration standardized management[10].

When recently published or about to be published CPGs for the treatment of acute diarrheal disease are analyzed, we find that, although most of them are consistent with regard to the recommendation of reduced-osmolarity oral rehydration solutions as the cornerstone of treatment and recommendations to a larger or lesser extent of other coadjuvant agents such as racecadotril, smectite, probiotics and zinc, most recommendations originate in separately-analyzed clinical trials or systematic reviews with meta-analyses assembled in a traditional manner, which practically entirely include direct comparisons of any of the above mentioned coadjuvants, with no indirect comparison analyses of these with each other having been conducted up to this moment[11-16].

In view of all of this, we decided to conduct a systematic review of evidence published until February 2014 and to present it as a meta-analysis of multiple treatments, with the purpose of making an integration of data through direct and indirect comparisons and, this way, being able to comprehensively summarize the information, trying to offer guidelines for cost-efficient decision making in this field.

## Methods

A systematized and thorough search was carried out in Medline, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), PsychINFO, the Cochrane Central Register of Controlled Trials, Lilacs, Artemisa and the clinical trial databases of the main international regulatory agencies in order to identify relevant studies published since 1960 and up to February 28, 2014. Previously validated sensitive and specific search algorithms were used[17] for identification of all clinical trials involving the use of racecadotril, smectite, *L.* GG, *L. reuteri, S. bolulardii* and zinc. All relevant authors were contacted, as well as manufacturers of the products under analysis in order to identify non-published data. Only double-blind, randomized, controlled trials (RCTs) comparing any of the aforementioned medications with placebo for in-hospital or outpatient treatment of acute diarrheal disease in children younger than 5 years were included. The primary outcome analyzed was duration of diarrhea (hours) after the treatment under evaluation was started, whereas secondary outcome measures were fecal output at 48-72 h of study and frequency of adverse events.

Assessment of the studies was made pair-wise, in a blinded and independent manner using the risk assessment method described by the Cochrane Collaboration[18,19]. Any disagreement on the evaluation of articles was solved using the Delphi methodology[20], which was always coordinated by the investigator responsible of the publication. According to the Cochrane Collaboration recommendations on systematic reviews preparation, a structured format was used to capture information in order to ensure the highest possible consistency. Obtained data were: general characteristics of the publication (first author, publication year, jornal of publication, setting where the investigation was conducted and type of funding), characteristics of participants (age, gender, underlying diseases, duration and severity of diarrheal symptoms before entering the study), received treatments (type of administered rehydration solutions, use of medications, dosing, duration of treatments) and analyzed outcomes.

Statistically, the information was analyzed using the multiple treatments meta-analysis approach. Considering that the common denominator of all studies was the use of placebo, we decided to use this maneuver as the central point for direct comparisons. Dichotomous outcomes were analyzed with the total number of randomly assigned participants as the denominator. For the secondary efficacy analysis, measured as binary outcomes, outcomes were imputed for participants' missing data, assuming that all patients with missing data were non-responders. When data on withdrawals was reported, these were included in the analysis. Descriptive statistics on population characteristics and its results was reported for each potentially eligible

study, describing the type of comparison and the most important clinical and methodological variables. For each paired comparison (direct or indirect), in the case of continuous numerical variables, Hedges' adjusted standardized mean difference (SMD) was calculated, whereas for dichotomous outcomes, their respective odds ratio was calculated, in both cases with the corresponding 95% confidence interval (95% CI). Initially, we prepared a pair-wise meta-analysis of all published studies. We used a random effect model considering that different studies estimated different treatment effects. Simultaneously, we calculated the I2-statistic and its corresponding p-value to objectively assess the degree of heterogeneity.

Subsequently, we assembled a multiple-treatment meta-analysis using a random effects model with a Bayesian approach[21,22] and summarized the results using the effect sizes and their credibility intervals. We used an adjustment model as described by Salanti, et al.[23].

Additionally, we calculated the superiority likelihood of each anti-diarrheal medication by means of a SUCRA analysis and presented it with a relative arrangement graph[24].

To estimate inconsistency (discordance between direct and indirect evidence with a 95% CI without including zero), we calculated the difference between direct and indirect estimates, using as reference only constructed indicators that would have included the use of placebo as common maneuver[25].

Additionally, we adjusted the model with and without consistency assumptions and compared both models in terms of goodness of fit and parsimony[26].

In case of significant inconsistence, we examined the distribution of clinical variables that could be potential source of heterogeneity or inconsistency within each group of specific comparisons. All analysis and graphical representations were performed in STATA 12 for Mac.

## Results

Of a total of 128 potential trials to be included, 50 RCT were finally included[27-77] in the multiple-treatment meta-analysis, and the nine treatment modalities were analyzed using them: racecadotril, smectite, *L.* GG at doses > $10^{10}$ colony-forming units (CFU), *L.* GG at doses ≤ $10^{10}$ CFU, *L. reuteri, S. boulardii,* zinc in > 6-month, zinc in ≤ 6-month children and placebo. All included studies compared two groups and had the comparison with placebo in common. When total included patients were added up, we identified that 5,391 chidren were assigned to placebo and 5,324 to any of the other medications. Average duration of the studies was 4.5 ± 1.3 days and average sample size was 90 ± 89 patients per study. With regard to clinical characteristics, the majority of studies included children with moderate to severe diarrhea; 54% of the studies were conducted in oral rehydration rooms, where children were invited to remain hospitalized in order to measure the fecal output rate, whereas the rest of the studies were conducted with outpatients. Except for the direct comparisons of each medication with placebo, the 56 comparisons between medications other than placebo were indirect (Fig 1).

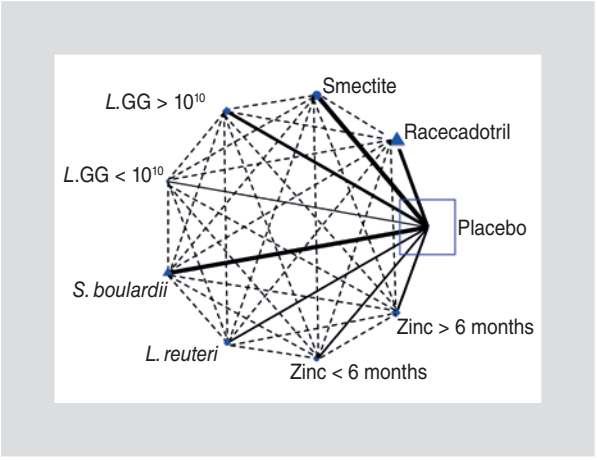


**Figure 1.** *Direct and indirect comparisons of coadjuvant agents in the treatment of acute diarrhea in children younger than 5 years.*

When the impact of medications and placebo on diarrhea duration was analyzed by means of direct comparisons, the meta-analysis demonstrated significant efficacy for practically all medications except for *L.* GG at doses < $10^{10}$ CFU and zinc in children younger than 6 months (Fig. 2, Table 1).

The multiple-treatment meta-analysis where both direct and indirect comparisons were assessed, identified superiority for racecadotril over the rest of coadjuvant agents, followed by smectite, and there was an apparent therapeutic equivalence between the different types of analyzed prebiotics when they were compared to each other; similarly, we identified therapeutic equivalence between the different types of prebiotics when they were compared with zinc administration in children older than 6 months (Fig. 3).

In order to demonstrate the consistency of both direct and indirect comparisons, a funnel plot modeling was used, and a very similar pattern of behavior was

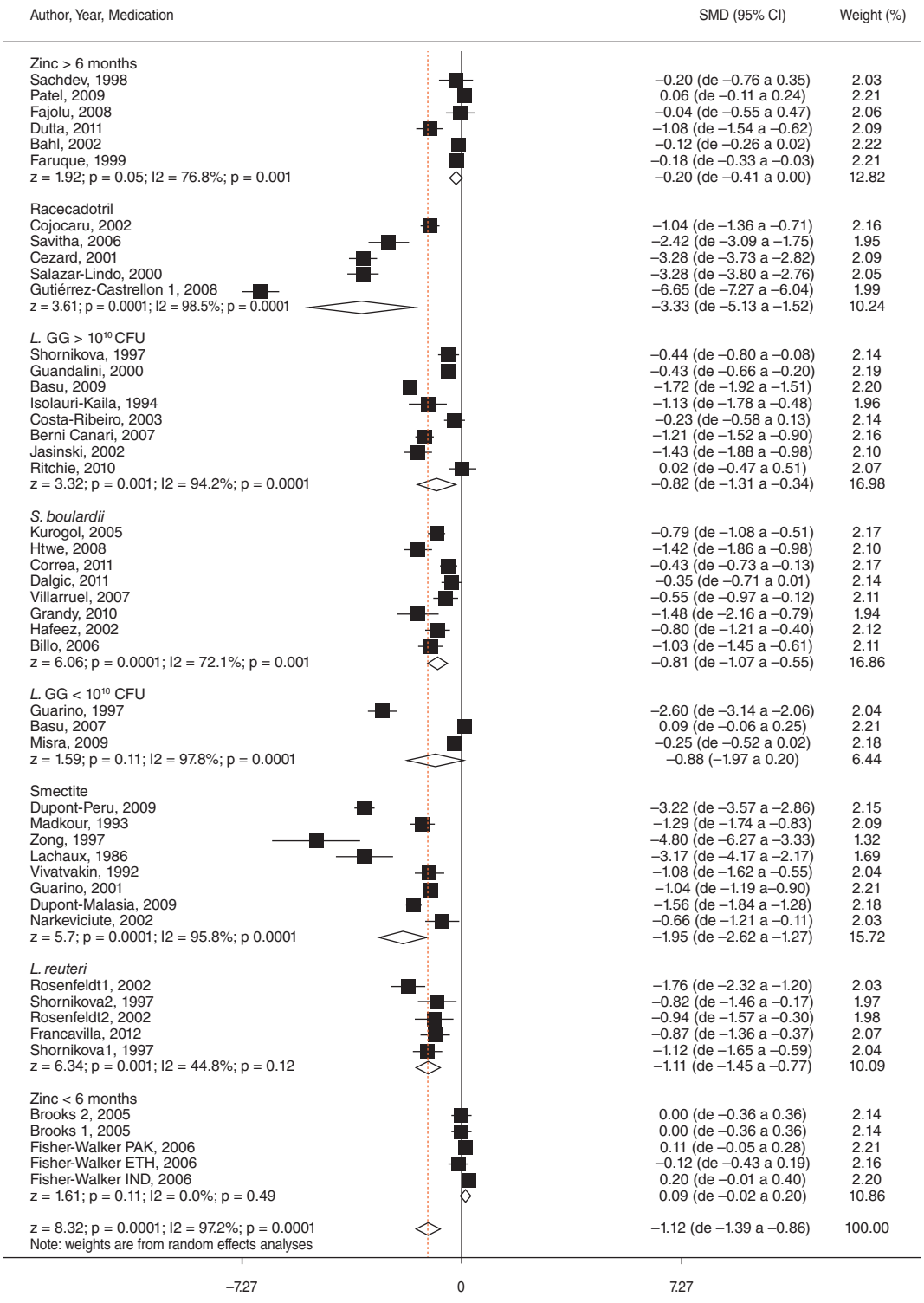


**Figure 2.** *Meta-analisis of direct comparisons.*

**Table 1. Characteristics of direct comparisons and their impact on diarrhea duration**

| Comparison | Active group (n) | Placebo group (n) | SMD (95% CI) | z-value (p) |
|---|---|---|---|---|
| Racecadotril vs. placebo | 699 | 685 | –3.33 (–5.13 to –1.52) | 3.61 (0.0001) |
| Smectite vs. placebo | 948 | 951 | –1.95 (–2.62 to –1.27) | 5.70 (0.0001) |
| *L.* GG > $10^{10}$ CFU vs. placebo | 1,129 | 1,315 | –0.82 (–1.31 to –0.34) | 3.32 (0.001) |
| *L.* GG ≤ $10^{10}$ CFU vs. placebo | | | –0.88 (–1.97 to 0.20) | 1.59 (0.11) |
| *S. boulardii* vs. placebo | 596 | 596 | –0.81 (–1.07 to –0.55) | 6.05 (0.001) |
| *L. reuteri* vs. placebo | 133 | 154 | –1.11 (–1.45 to –0.77) | 6.34 (0.001) |
| Zinc vs. placebo (≤ 6 months) | 625 | 709 | 0.09 (–0.02 to 0.20) | 1.61 (0.11) |
| Zinc vs. placebo (> 6 months) | 1,086 | 1,089 | -0.20 (–0.41 to 0.00) | 1.92 (0.05) |

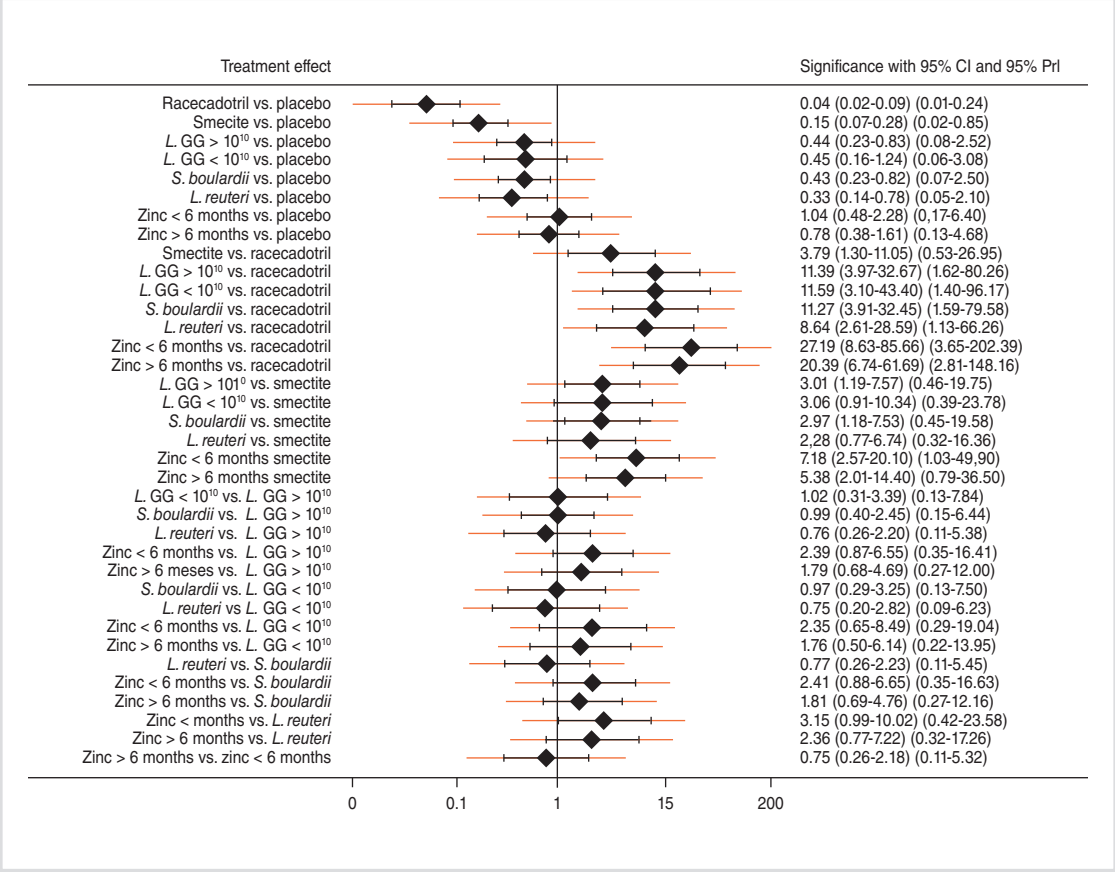


**Figure 3.** *Meta-analysis of direct and indirect comparisons of coadjuvant agents in the treatment of acute diarrhea in children younger than 5 years.*

identified between studies, with similar differences when both the size of effect of the standard error and the effect of specific comparisons were observed, which allows for the robustness of the model and the conclusions indicated in the multiple-treatment meta-analysis to be supporterd (Fig. 4).

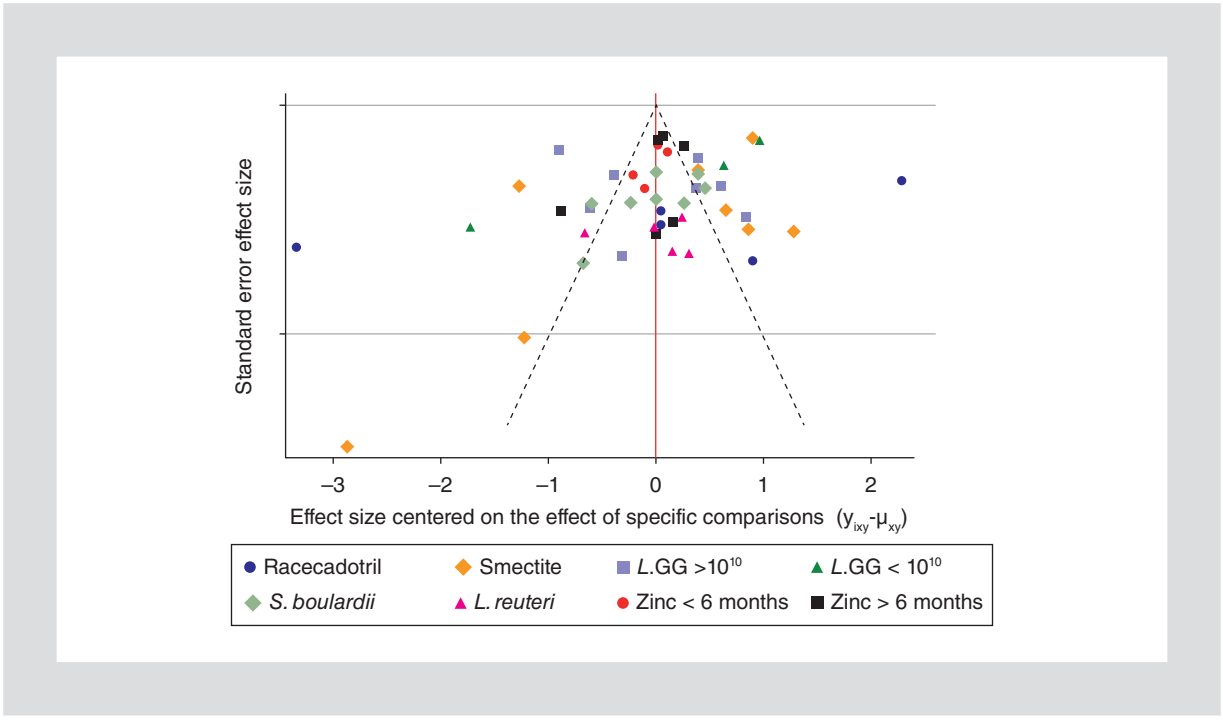


**Figure 4.** *Funnel plot of multiple comparisons.*

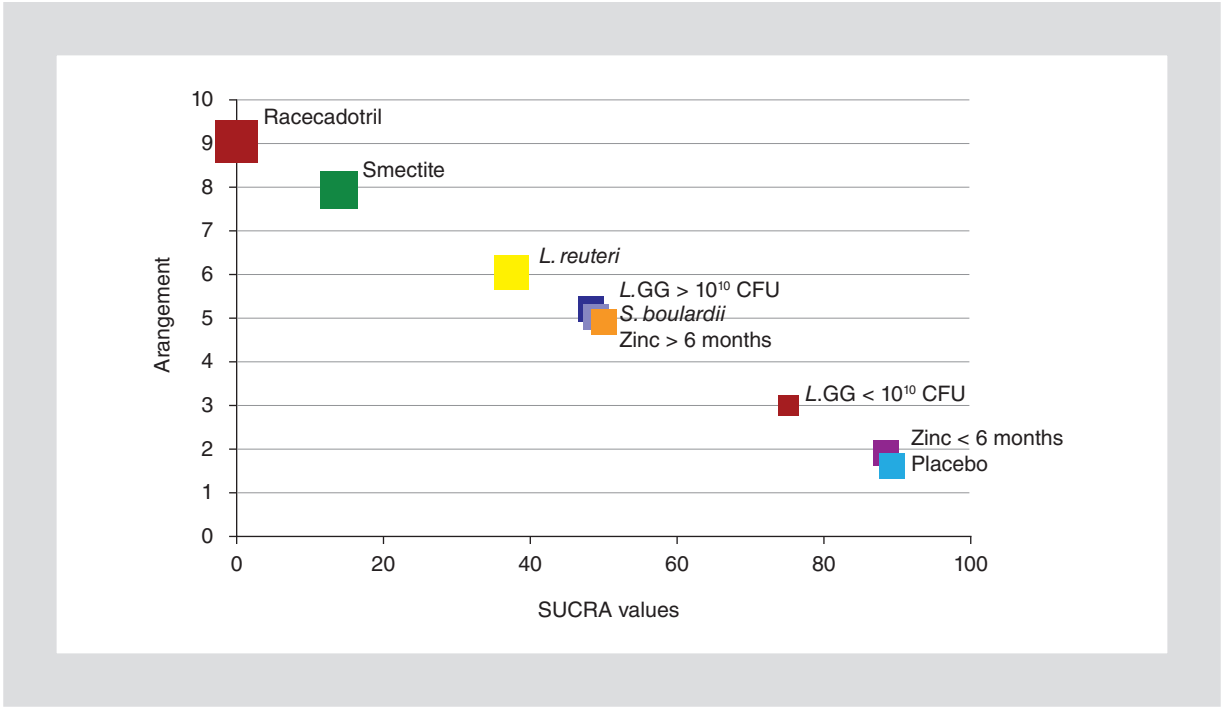


**Figure 5.** *Best treatment assesment.*

Finally, using data of the previous analyses both from direct and indirect comparisons, we established a relative arrangement model using the SUCRA command of STAT 12.0 in order to identify the first best treatment according to the analyzed primary outcome, and we indentified racecadotril as being at first place, with a value of 9.0, followed by smectite (7.0) and, in third place, *L. reuteri* (6.0) (Fig. 5).

## Discussion and conclusions

Acute gastroenteritis remains as an important cause of morbidity and mortality among children, especially in countries with limited resources. Although there is a significant proportion of mild and self-limited cases, it represents an important cause for hospitalization and is associated with significant burden of disease[78,79].

Analyzed from a global perspective, it acquires a huge importance from the public health point of view if we consider that it generates approximately 20% of all deaths ocurring in children younger than 5 years in the world[80].

Despite the intense promotion to consider oral rehydration solutions as the cornerstone of treatment, less than 20% of children with acute gastroenteritis are estimated to optimally receive a preventive or therapeutic regimen for this type of problems, which entails high rates of hospitalization, complications, long hospital stays and significantly high direct and indirect costs[81]. So, only in the USA, this disease is estimated to generate 1.5 million visits to the doctor/year, 220,000 hospitalizations (10% of all hospital admissions in USA) and very significant figures of school and workplace absenteeism[82].

Even though oral hydration regimens with reduced osmolarity solutions continue to be regarded as the cornerstone of treatment, all this has motivated to increasingly insist on the need for therapeutic coadjuvants based on scientific evidence with methodological rigour that allow, in an additive or synergistic manner, evolution of this type of conditions to be favored and, therefore, complications, mortality and hospitalizations to be reduced, as well as the associated economic impact[83].

Unlike previous publications, including traditional systematic reviews with meta-analyses of pair-wise comparations that generally have made contrasts of different adjuvant agents with placebo, the originality of the present proposal lies in the fact that it includes analyses not only of direct comparisons (coadjuvant agent vs. placebo), but even of unpublished or indirect comparisons (e.g., racecadrotil vs. smectite; smectite vs. *L. reuteri*), which robustly allow for decision-making policies on the best coadjuvant therapy or therapies to be established[84-88].

The results of this multiple-comparison meta-analysis allow, first of all, to observe the effect of different coadjuvant agents when compared with placebo, but at the same time they allow, in second place, to graphically and mathematically visualize the effects generated when indirect comparisons of coadjuvants to each other are performed, thus immediately identifying the superiority that in the first place racecadotril can have, followed by smectite and then the therapeutic equivalence of other coadjuvant agents with each other, such as the administration of *S. boulardii, L. reuteri* at high doses (> $10^{10}$ CFU), *L. reuteri* or zinc in children older than 6 months. In parallell and concordantly, by performing the SUCRA analysis, which in one way or another weighs the number of published trials, the sample size in each one of them and within the type of coadjuvant agent, methodological quality of the designs, as well as significance and robustness of the reported results, we can confirm the superiority of racecadotril as a coadjuvant for the management of this condition, closely followed by the administration of smectite or *L. reuteri.* We consider that this type of analysis and results are significantly useful for the decision-maker in order to, under cost-effectiveness and risk-benefit criteria, be able to objectively rely on for an efficient health-related decision-making process.

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