Comment on "Efficacy of hypertonic saline versus isotonic saline among children with cystic fibrosis: A systematic review and meta-analysis"

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R Gutierrez-Arias, M-J Oliveros, P Seron. Response: Comment on "Efficacy of hypertonic saline versus isotonic saline among children with cystic fibrosis: A systematic review and meta-analysis". Can J Respir Ther 2023;59:100–102. doi: 10.29390/cjrt-2023-013.

We have read with interest the study by Ullah et al. [1], which found that inhaled hypertonic saline (HS) treatment significantly improves the lung clearance index (LCI), symptoms, lung function and quality of life in children affected by cystic fibrosis (CF) compared with isotonic saline (SI), which would support the use of this intervention in this population. These conclusions were reached by conducting a systematic review (SR), including seven clinical trials with 390 participants.

Intervention SRs are an evidence synthesis that aims to answer pre-defined research questions using explicit, reproducible methods to identify, critically appraise and combine results of primary research studies aimed at determining the effectiveness of any intervention on different health conditions [2].

One of the most significant values of this type of synthesis is that it helps the usually busy clinician to resolve dilemmas in their practice. In this sense, SR authors should be cautious when their findings lead to a recommendation for clinical practice. This is why, after reading the results and conclusions of this SR, we asked ourselves: How confident can we be that HS versus IS improves LCI, symptoms, lung function and quality of life in children with CF? Could limitations in study design and execution be biased in the treatment effect estimates? Could there be unexplained heterogeneity in the results? Did all the evidence compare the interventions they were interested in and conduct in the population they were interested in? Was the optimal information size reached? Was the confidence interval (CI) around the estimated effect too wide to cross critical clinical effect thresholds? And, was there an underestimation or an overestimation of the underlying beneficial or harmful effect due to the selective publication of studies? [3].

To explore whether these factors would change the conclusions that the authors of this review present, it is necessary to assess the certainty of the body of evidence, which can be performed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [4]. This framework states that evidence based on randomized controlled trials (RCTs) begins as high-quality evidence. Still, our confidence in the evidence may be decreased for several reasons, as well as the limitations of the studies, inconsistency of results, indirectness of evidence, imprecision and reporting bias [4].

To do that, we have assessed the certainty of the evidence using the GRADE framework, which we show in a "Summary of Findings" table (SoF table) (Table 1). This was performed by one researcher and reviewed by two others. Disagreements were resolved by consensus. We used the data from the intervention effect estimation and the risk of bias (RoB) assessment from the studies reported by Ullah et al. [1].

For lung function, we used only the absolute values and not the percentages of the predicted values, considering that these could have been analyzed in a pooled manner by calculating the standardized mean difference (SMD). In addition, to assess the quality of life, we consider 4 points as the minimum clinically important difference (MCID) to determine the imprecision of the effect estimate [9]. This approach was not considered for the other outcomes because we did not identify studies that reported MCID thresholds. Regarding the (RoB) assessment of the primary studies included, the SR of Ullah et al. [1] performs this step using a widely used tool such as the one proposed by Cochrane [10], which already presents a second version [11]. Ullah et al. [1] rated the "blinding of outcome assessment" domain for the studies by Amin et al. [5] and Subbarao et al. [6] as a high RoB, high RoB for the "incomplete outcome data" domain in the study by Stahl et al. [7], and high RoB for the "other bias" domain in the study by Rosenfeld et al. [8].

Therefore, considering the certainty of the evidence, our confidence in the estimated effect of HS versus IS in children with CF is at least limited, so the true effect of HS may be substantially different from the estimate of the effect by the review of Ullah et al. [1]. Consequently, it is preferable to give research recommendations in cases of low or very low certainty of the evidence and to increase the number of primary studies of improved quality to assess the possibility of recommending this intervention for most children with CF.

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TABLE 1
Summary of findings

Outcome	Estimated effect (95% CI) – Change before-after HS compared IS	N° of participants	Certainty	Reasons for downgrading the certainty of the evidence
Lung clearance (LCI)	MD **0.67 lower** (1.05 lower to 0.29 higher)	234 (4 studies)	⊕⊕⊖⊖ Low	The certainty of the evidence was downgraded by one level for the limitations of the studies included in the meta-analysis [5–7] and one level for imprecision due to the low number of total participants included.
Lung function (FEV_1)	MD **0.11 higher** (0.21 lower to 0.43 higher)	66 (3 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for limitations of the studies included in the meta-analysis [5] and two levels for imprecision due to the low number of total participants included and the CI limits favouring HS or IS.
Lung function (FVC)	MD **0.27 higher** (0.49 lower to 1.04 higher)	43 (2 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for limitations of the studies included in the meta-analysis [5] and two levels for imprecision due to the low number of total participants included and the CI limits favouring HS or IS.
Lung function (FEF_{25-75})	MD **0.12 higher** (0.05 higher to 0.20 higher)	364 (3 studies)	⊕⊕⊖⊖ Low	The certainty of the evidence was downgraded by one level for the limitations of the studies included in the meta-analysis [5, 8] and one level for imprecision due to the low number of total participants included.
Oxygen saturation (%)	MD **0.15 lower** (0.54 lower to 0.25 higher)	361 (2 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for limitations of the studies included in the meta-analysis [7, 8], and two levels for imprecision due to the low number of total participants included and the CI limits favouring HS or IS.
Respiration rate (rpm)	MD **0.40 lower** (2.19 lower to 1.77 higher)	361 (2 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for limitations of the studies included in the meta-analysis [7, 8], and two levels for imprecision due to the low number of total participants included and the CI limits favouring HS or IS.
Height (cm)	MD **2.23 higher** (0.00 lower to 4.46 higher)	361 (2 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for limitations of the studies included in the meta-analysis [7, 8], and two levels for imprecision due to the low number of total participants included and the CI limits favouring HS or IS.
Weight (kg)	MD **0.70 higher** (0.47 lower to 1.87 higher)	361 (2 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for limitations of the studies included in the meta-analysis [7, 8], and two levels for imprecision due to the low number of total participants included and the CI limits favouring HS or IS.
Quality of life (CFQ-R)	MD **4.3 higher** (0.65 higher to 7.95 higher)	363 (3 studies)	⊕⊖⊖⊖ Very low	The certainty of the evidence was downgraded by one level for the limitations of the studies included in the meta-analysis [5, 8] and two levels for imprecision due to the low number of total participants included and the lower limit of the 95% CI being less than the minimum clinically important difference (4 pts).

CI = Confidence intervals; HS = Hypertonic saline; IS = Isotonic saline; LCI = Lung clearance index; MD = Means difference; RoB = Risk of bias; FEV^1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; FEF^{25-75} = Forced expiratory flow over the middle one-half of the FVC; rpm = Respirations per minute; CFQ-R = Cystic Fibrosis Questionnaire-Revised.

NOTE: GRADE Working Group grades of evidence
⊕⊕⊕⊕ ***High certainty:*** *We are very confident that the true effect lies close to that of the estimate of the effect.*
⊕⊕⊕⊖ ***Moderate certainty:*** *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕⊖⊖ ***Low certainty:*** *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕⊖⊖⊖ ***Very low certainty:*** *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.*

DISCLOSURES

Contributors
RG-A, M-JO and PS contributed to the conception of the work and the acquisition, analysis and interpretation of the data.

Funding
The present study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests
No financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval
Not applicable.

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