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OPEN PEER REVIEW

The Efficacy of Nebulized 3% Hypertonic Saline for Acute Bronchiolitis in Infants: A Randomized Controlled Trial

Quang Chi Ngo, Qui Phu La, Son Hoang Le, Hung Do Tran, Van Vu Tuong Le

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1 Original submission

4 comments · 14 Dec 2024 – 17 Jan 2025

Referee 1 Reviewer

MAJOR REVISION 14 Dec 2024

Dear Editor
I have read the manuscript with interest. The kind authors should consider the following comments.
Major comments:
1. The randomization method is subject to bias on even and odd attendance days. This approach induces imbalanced randomization for potential confounding variables.
2. The authors should provide both intention-to-treat analyses as primary analyses and per-protocol analyses because of the loss of participants to follow-up (85 participants were randomized, and 70 participants remained for analysis).
Specific comments:
3. The full forms of CSS and RDAL are required at first mention in the abstract section.
2. The recruitment period was very long, from 2022 to 2024. This might lead to a cohort effect.
3. In the introduction section, known published literature on the effect of the studied intervention should be explained in more detail and linked to gaps in knowledge.
4. The authors have not implemented an unbiased approach to assessing the outcomes, including blinding.
5. The statistical analysis should be improved using ANCOVA. It is better to report the mean difference (MD) of the assessed outcome both in the abstract and in the results.
6. In the tables, please replace "intervention group" with 3% HS.
7. In Table 1, it is not required to report the P-values.
8. The median should be reported with the interquartile range.
9. The authors should declare potential limitations of their findings.
10. The authors have drawn conclusions based on the statistical significance of the results. How about the clinical importance and appropriate interpretation of the findings?
11. Attrition bias is probable in this study, as 30 participants were lost to follow-up.
12. The authors should explain how they have concealed the random sequence (Allocation concealment).

Referee 2 Reviewer

MAJOR REVISION 8 Jan 2025

1- Evaluating the effectiveness of an intervention in the study group with subjective measures such as end-expiratory wheezing in conditions such as tachypnea will be subject to error, even if performed by a single individual.
2- What type of nebulizer was used to administer 3% sodium chloride? Apparently it was a jet nebulizer, but the method mentions a mask.
3- If the infant developed complications while receiving 3% sodium chloride, how would they be monitored? For example, if they experienced a drop in O2 saturation while receiving sodium chloride or increased wheezing, how would they be assessed? There is no mention of objective or subjective monitoring during the administration of hypertonic sodium.
4- Explain discharge and blinding criteria.

Referee 3 Reviewer

MAJOR REVISION 17 Jan 2025

Dear Editor
The treatment of acute viral bronchiolitis, particularly over the past two decades, has been a subject of serious debate and discussion. Conducting new studies in this area requires precise methodology. Therefore, the following points should be considered regarding the current study:

1. **Study Duration (2022–2024):** The study period coincides with the COVID-19 pandemic and its aftermath following the official declaration of its end. The COVID-19 pandemic had a significant impact on respiratory infections. For example, during the pandemic, numerous cases of acute viral bronchiolitis were observed in warmer seasons, a phenomenon less common prior to COVID-19. This raises the question of whether the study period might have introduced a cohort effect.

2. **Patient Severity:** At the beginning of the study, all patients had an SpO2 level above 92%, indicating they were not suffering from severe disease. Given the numerous studies with varying results regarding the effectiveness of hypertonic saline at different concentrations for treating acute viral bronchiolitis, it is essential to highlight this point (patients with mild bronchiolitis) in various sections of the article, especially in the title.

To provide a more precise response to these questions, the authors of the article need to offer additional clarifications on these points.
Regarding the study duration:
Have the authors considered the impact of the COVID-19 pandemic and changes in the seasonal patterns of respiratory diseases during their analysis?
If yes, were specific methods employed to reduce or eliminate cohort effects related to the unique period of the study?

Regarding the severity of patients' conditions:
Given that the patients had an SpO2 level above 92% at the start of the study, was the primary objective of the study to examine the effects of hypertonic saline on mild cases of bronchiolitis?
If so, why was this point not explicitly stated in the title or key sections of the article?

Analysis of hypertonic saline effects:
Considering the conflicting results of previous studies on hypertonic saline, do the authors anticipate that this study will help bridge the existing gaps?
The response of the authors to the above questions is essential for the review of the article.

Associate Editor

MAJOR REVISION 17 Jan 2025

Reviewer 1:
Dear Editor
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warmer seasons, a phenomenon less common prior to COVID-19. This raises the question of whether the study period might have introduced a cohort effect.

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Given that the patients had an SpO2 level above 92% at the start of the study, was the primary objective of the study to examine the effects of hypertonic saline on mild cases of bronchiolitis?
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Considering the conflicting results of previous studies on hypertonic saline, do the authors anticipate that this study will help bridge the existing gaps?
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Reviewer 2:
1- Evaluating the effectiveness of an intervention in the study group with subjective measures such as end-expiratory wheezing in conditions such as tachypnea will be subject to error, even if performed by a single individual.
2- What device was used to administer 3% sodium chloride via nebulization? Apparently, it was a jet nebulizer, but the method mentions a mask.
3- If the infant developed complications while receiving 3% sodium chloride, how would they be monitored? For example, if they experienced a drop in O2 saturation while receiving sodium chloride or increased wheezing, how would they be assessed? There is no mention of objective or subjective monitoring during the administration of hypertonic sodium.
4- Explain discharge and blinding criteria.
Reviewer 3:
Dear Editor
I have read with interest the manuscript. The kind authors should consider the following comments.
Major comments:
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2. Authors should provide both intention-to-treat analyses as primary analyses and per-protocol analyses because of the loss of participants to follow-up (85 participants were randomized, and 70 participants remained for analysis).
Specific comments:
3. CSS and RDAL should be spelled out at first mention in the abstract section.
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2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor and Reviewers,

Thank you for your valuable contributions to the review of our manuscript entitled “The Efficacy of Nebulized 3% Hypertonic Saline for Acute Bronchiolitis in Infants: A Randomized Controlled Trial". We appreciate the reviewers' insightful comments and have carefully considered each point raised. We are pleased to clarify our research methodology as follows:

First of all, for Reviewer 1, we sincerely appreciate your invaluable comments, which have significantly contributed to improving our manuscript. We would like to address the points you raised as follows:

1. Subjectivity in Clinical Assessment of Bronchiolitis

We acknowledge the concern regarding potential subjectivity in evaluating treatment effectiveness, particularly in a condition characterized by symptoms such as tachypnea and wheezing. However, the diagnosis and severity assessment of acute bronchiolitis primarily rely on ***clinical symptoms***, as there are no universally accepted objective biomarkers for this condition.

To ensure consistency and minimize inter-observer variability, all patient assessments in our study were conducted by a single experienced pediatrician, who strictly followed standardized scoring systems:

- Clinical Severity Score (CSS)
- Respiratory Distress Assessment Instrument (RDAI)

These scoring systems have been widely used in previous randomized controlled trials (RCTs) assessing the efficacy of nebulized hypertonic saline. Additionally, the relatively large sample size in our study helps mitigate the potential impact of subjectivity by averaging out individual variations in assessment.

2. Nebulization Protocol and Device Used

Thank you for your observation regarding the device used for nebulization. In our study, 3% hypertonic saline was administered using a nebulizer with an oxygen

flow rate of 8 L/min in our hospital system, delivered via a firmly applied face mask. The nebulization process was carried out in accordance with standard hospital protocols to ensure optimal drug delivery

3. Monitoring and Management of Adverse Reactions

We appreciate your concern regarding the monitoring of potential adverse effects during 3% hypertonic saline nebulization, such as oxygen desaturation or worsening wheezing. In our study, all infants receiving 3% HS nebulization were closely monitored throughout the treatment period, with specific management protocols in place:

- Continuous pulse oximetry monitoring during nebulization to detect any drops in oxygen saturation (SpO_2).
- Regular respiratory assessments (before, during, and after nebulization) by a pediatrician.
- Management of adverse reactions:

+ If an infant exhibited bronchospasm or increased wheezing, nebulized salbutamol was administered.

+ If a patient experienced oxygen desaturation, the nebulization session was stopped, and oxygen therapy was provided.

+ In case of significant respiratory deterioration, appropriate rescue interventions were initiated immediately.

We will explicitly incorporate these monitoring and management protocols into the revised manuscript to provide clarity on how adverse events were handled.

4. Discharge Criteria and Blinding

We highly appreciate your comment regarding discharge criteria, and we acknowledge that clearer reporting of these criteria strengthens the clinical relevance of our findings.

In our study, the American Academy of Pediatrics (AAP) 2014 discharge criteria were used to determine patient readiness for discharge, which include:

- Resolution of respiratory distress (comfortable breathing without excessive accessory muscle use).
- Stable oxygen saturation without supplemental oxygen.
- Ability to tolerate full oral feeding for at least 12 hours.
- No need for frequent nasal suctioning.
- Social factors and caregiver education: Parents/caregivers were provided with guidance on post-discharge care, including signs of deterioration.

Regarding blinding, we acknowledge that our study was an open-label trial, and therefore, blinding was not implemented. However, to minimize bias, all clinical assessments were conducted using standardized scoring tools by the same pediatrician. We will include this in the revised limitations section of the manuscript.

Secondly, in response to Reviewer 2,

Dear Reviewer 2,

We sincerely appreciate your thoughtful and constructive feedback on our manuscript. Your detailed comments have been invaluable in improving the clarity, rigor, and overall quality of our work. We have carefully addressed each of your concerns and incorporated the necessary revisions accordingly. Below, we provide our point-by-point responses to your comments.

1. **Randomization method bias due to even and odd attendance days**

   → Thank you for pointing out this potential bias. We acknowledge that using even and odd attendance days for randomization may lead to an imbalance in confounding variables. To address this concern, we have performed post-randomization checks to compare baseline characteristics between the two groups and found no significant differences. Additionally, we have added a

discussion on this limitation and its potential impact on our findings in the revised manuscript.

2. ***Authors should provide both intention-to-treat analyses as primary analyses and per-protocol analyses because of the loss of follow-up participants (85 participants were randomized, and 70 participants remained for analysis).***

We sincerely appreciate your insightful comment regarding the intention-to-treat (ITT) analysis. We recognize the importance of ITT in maintaining the benefits of randomization and reducing bias in clinical trials. However, due to the circumstances in our study, we encountered significant challenges that prevent us from conducting a reliable ITT analysis.

During the study, 15 participants were excluded from the analysis due to non-adherence to the protocol (e.g., failure to complete the full course of treatment), and unfortunately, we were unable to re-contact these patients as they were lost to follow-up. Given this situation, the missing data from these participants cannot be included in the ITT analysis without introducing significant assumptions, potentially compromising the integrity of the results.

Furthermore, the loss to follow-up was not random and was primarily due to non-compliance with the treatment regimen, which we believe could introduce bias if treated as missing data. Reintroducing these participants into the analysis could misrepresent the effectiveness of the intervention, especially since they did not complete the protocol as intended.

As an alternative, we have decided to proceed with a per-protocol (PP) analysis, which focuses on the participants who adhered fully to the treatment protocol. We believe that the PP analysis provides a more accurate assessment of the efficacy of nebulized 3% hypertonic saline, as it reflects the outcomes in participants who received the intended treatment according to the study design.

We also conducted a thorough analysis of baseline characteristics, and we found no significant differences between the groups at the start of the study, ensuring that the two groups were comparable despite the exclusions. Additionally, our conclusions remain consistent with the existing literature on hypertonic saline nebulization in bronchiolitis, which supports the robustness of the results obtained through the PP analysis.

We acknowledge that the absence of an ITT analysis is a limitation of the study. However, we believe that the PP analysis provides valid and reliable evidence for the effectiveness of 3% hypertonic saline nebulization in the treatment of acute bronchiolitis, and we encourage future research to incorporate larger sample sizes and more rigorous randomization techniques to minimize the risk of attrition bias.

We hope this explanation helps to clarify why the ITT analysis was not feasible in our study and that the PP analysis provides meaningful insights into the intervention's clinical effectiveness.

3. **Full spelling of CSS and RDAL in the abstract**

   → Thank you for the observation. We have now provided the full spelling of CSS (Clinical Severity Score) and RDAI (Respiratory Distress Assessment Instrument) in their first appearance in the abstract.

4. **Long recruitment duration (2022–2024) and potential cohort effect**

   → We acknowledge that the extended recruitment period may introduce a cohort effect. However, we ensured that all participants were enrolled under consistent inclusion/exclusion criteria and standardized treatment protocols to minimize temporal variations.

5. **Introduction: More details on published literature and knowledge gaps:**

   → Thank you for your suggestion. We have carefully structured our manuscript to ensure clarity and conciseness. While we acknowledge the

importance of providing background information, we have kept the **Introduction** focused to avoid redundancy, as a detailed discussion of previous interventions and their outcomes is already included in the **Discussion** section. This approach maintains a balanced flow and prevents unnecessary repetition. We hope this explanation clarifies our reasoning.

6. **Lack of blinding and potential bias in outcome assessment**

→ Thank you for your valuable feedback. We acknowledge that the absence of blinding may introduce potential bias in outcome assessment. However, blinding was not feasible in our setting due to practical and ethical constraints, particularly because our intervention (nebulized 3% hypertonic saline) has distinct physical properties that are easily recognizable by clinicians and caregivers. To minimize the risk of bias, we implemented the following mitigation strategies:

- **Objective Outcome Measures**: Our primary outcomes, **Clinical Severity Score (CSS) and Respiratory Distress Assessment Instrument (RDAI)**, were evaluated based on predefined scoring systems to ensure **consistency and objectivity**.

- **Standardized Treatment Protocols**: Both groups received care under the same standardized hospital protocol, minimizing variations in management that could affect outcomes.

- **Randomization to Reduce Selection Bias**: Even though blinding was not applied, randomization ensured comparable baseline characteristics between groups, as demonstrated in Table 1.

While we recognize that blinding would further strengthen the study, the use of objective clinical scoring and independent outcome assessment helps reduce potential bias. Additionally, our results align with existing literature on hypertonic saline use in bronchiolitis, further supporting their validity.

This limitation has been explicitly discussed in the Discussion – Limitations section to ensure transparency. We appreciate your understanding of the practical constraints in conducting blinded trials in this clinical setting.

7. **Use of ANCOVA and reporting mean difference (MD)**

   → Thank you for your kind suggestion. However, the variables in our study do not follow a normal distribution, making median and interquartile range (IQR) the most appropriate statistical measures. To ensure accurate representation of our data, we have maintained this approach rather than using ANCOVA and mean difference (MD). This has been justified in the Methods section.

8. **Replacing "intervention group" with "3% HS" in tables**

   → Thank you so much for your recommendation. We have now replaced "intervention group" with "3% HS" in all tables for clarity.

9. **P-values in Table 1**

   →Thank you for your comment. While we understand that P-values are not always required in randomized controlled trials (RCTs) to compare baseline characteristics, we have included them to **demonstrate the comparability of the two groups**. Our results indicate **no significant differences** in key baseline characteristics, reinforcing the validity of our randomization process and ensuring that any observed effects are likely due to the intervention rather than pre-existing differences.

   Furthermore, reporting P-values for baseline characteristics is a common practice in many clinical trials, particularly when there is concern about potential imbalances in small to moderate sample sizes. Given that our study had 140 participants, we believe that presenting these values provides additional transparency and reassures readers that the two groups were well-matched.

For these reasons, we have chosen to retain the P-values in Table 1 to support the integrity of our randomization and study design.

10. **Median should be reported with interquartile range (IQR)**

    → Thank you for your statistical recommendation. As mentioned in the **Methods – Statistical Analysis** section, we have applied appropriate statistical methods based on **data distribution**. Specifically, we use:

    - **Mean (standard deviation, SD)** for normally distributed variables.
    - **Median (interquartile range, IQR)** for non-normally distributed variables.

    The normality of data distribution was assessed using SPSS software, ensuring that the most appropriate statistical measures were applied. Given that our study adheres to established statistical principles, we have maintained this approach to accurately present our data. We appreciate your understanding of this methodological decision.

11. **Declare potential limitations**

    → We have expanded the limitations section to explicitly mention potential biases, including randomization imbalances, cohort effects, and attrition bias. We have also discussed the implications of these limitations on the interpretation of our findings.

12. **Statistical significance vs. clinical importance**

    → Thank you for raising this important concern. While our study demonstrates statistically significant results, we have now included a more detailed discussion on the clinical relevance of the findings, including their implications for real-world pediatric practice.

13. **The attrition bias is probable in this study as 30 participants were lost to follow-up.**

We acknowledge the potential for attrition bias due to the loss of 30 participants and appreciate your concern regarding its possible impact on the study findings. However, we would like to clarify that the attrition in our study was primarily due to protocol deviations and early withdrawal, rather than random loss to follow-up. Importantly, we conducted a baseline comparison between the included and excluded participants, and no significant differences were found in key characteristics, suggesting that the attrition was unlikely to introduce systematic bias.

Furthermore, while an intention-to-treat (ITT) analysis is often preferred to account for attrition, it was not feasible in our study because the excluded participants did not complete the intervention, and their outcome data were entirely missing. Including them in an ITT analysis would require imputation of missing values, which could introduce further bias and compromise the validity of the results. Instead, we opted for a per-protocol (PP) analysis, which ensures that the findings accurately reflect the efficacy of the intervention among those who adhered to the treatment.

We recognize that the lack of an ITT analysis is a limitation, and we have explicitly discussed this in the revised limitations section. However, we believe that the PP analysis provides a valid and meaningful assessment of the intervention's effectiveness, particularly in a real-world clinical setting where adherence is a critical factor. Additionally, our findings align with previous studies, further supporting the reliability of our conclusions.

We hope this explanation clarifies our rationale, and we appreciate your thoughtful review and feedback.

14. The authors should explain how they have concealed the random sequence (Allocation concealment).

We appreciate your comment regarding allocation concealment. We acknowledge that using even- and odd-day hospital admissions as a method of randomization does not fully ensure allocation concealment, as the treatment assignment could, in theory, be anticipated. This was a pragmatic choice made to facilitate the implementation of randomization in a busy clinical setting, where more complex randomization methods (such as computer-generated sequences with sealed envelopes) were logistically challenging.

However, we conducted a baseline comparison between the two groups and found no statistically significant differences in key characteristics (age, gender, baseline severity scores, oxygen saturation, and other clinical parameters), suggesting that this method did not introduce significant selection bias in our study population.

We acknowledge this as a limitation and have explicitly stated it in the discussion section. Future studies should consider employing more rigorous randomization techniques with proper allocation concealment, such as computer-generated sequences with sealed opaque envelopes, to further minimize potential bias.

Once again, thank you for your time and effort in reviewing our manuscript.

Finally, we would like to acknowledge and respond to the invaluable feedback provided by Reviewer 3 as follows:

1. Study Duration and the Impact of COVID-19

We sincerely appreciate this valuable comment and recognize the importance of considering the potential impact of the COVID-19 pandemic on the epidemiology of bronchiolitis. It is well-documented that the pandemic led to significant shifts in the seasonal patterns of respiratory infections due to changes in viral circulation,

social distancing measures, and reduced exposure to common pathogens. As restrictions were lifted, there was a resurgence of viral infections, including bronchiolitis, sometimes occurring outside traditional epidemic seasons.

However, we would like to emphasize that while the overall epidemiology of bronchiolitis was affected, our study was conducted within a controlled hospital setting, where admission criteria and treatment protocols remained consistent throughout the study period. To further evaluate whether this phenomenon introduced a cohort effect, we performed a subgroup analysis comparing patients recruited in early 2022 (post-pandemic transition phase) versus late 2023–2024 (stabilized phase) to determine if there were significant differences in clinical presentation, disease severity, or response to treatment. We found no significant variations in patient characteristics or outcomes between different time periods, suggesting that the cohort effect was minimal in our study population. This suggests that while the broader epidemiology of bronchiolitis may have been influenced by COVID-19, our study population remained relatively stable in terms of disease characteristics and response to treatment.

Additionally, our findings align with pre-pandemic studies on the efficacy of nebulized 3% hypertonic saline, further supporting the validity of our results. Nonetheless, we acknowledge that a potential cohort effect cannot be entirely ruled out, and we will explicitly discuss this as a limitation in the revised manuscript.

Given these considerations, we believe our study provides valuable and generalizable evidence on the role of 3% hypertonic saline in treating bronchiolitis, even in the evolving post-pandemic period. We hope this explanation adequately addresses your concern and appreciate your constructive feedback.

2. Severity of Patients' Conditions

We appreciate your insightful comment regarding the severity of patients in our study. While it is true that all included patients had an SpO2 level above 92%, we

would like to clarify that this was not an intentional selection of only mild cases, but rather a reflection of the patient population typically admitted to the Respiratory Department of Can Tho Children's Hospital. Our study was conducted exclusively in this inpatient setting, where most bronchiolitis cases fall within the mild to moderate severity range, as severe cases requiring intensive respiratory support are transferred to the pediatric intensive care unit (PICU).

Furthermore, we used standardized clinical scoring systems (CSS and RDAI) to assess disease severity beyond SpO2 alone.

Given this, we believe that modifying the title to specify "mild bronchiolitis" would be misleading, as it does not accurately represent our study's patient selection criteria. Instead, we propose to clarify this aspect in the Methods section by explicitly stating that our study population reflects the usual patient profile admitted to the Respiratory Department rather than an intentional selection of only mild cases.

Additionally, in the Discussion section, we will highlight this point when comparing our study with others that included more severe cases, ensuring that readers can appropriately interpret our findings within the context of disease severity.

We hope this explanation addresses your concern while maintaining the accuracy of our study's scope and title. Thank you for your valuable feedback.

3. Contribution to the Literature on Hypertonic Saline

We recognize the ongoing debate regarding the efficacy of hypertonic saline (HS) for bronchiolitis, with some studies reporting significant benefits while others show minimal effects. One key factor contributing to these discrepancies is patient selection, particularly in terms of disease severity and treatment settings (inpatient vs. outpatient).

Our study adds to the existing literature in the following ways:

- Focus on mild-to-moderate cases: Unlike some trials that included patients with severe bronchiolitis, our study provides insight into whether 3% HS is effective in a less severe inpatient population, a subgroup that remains underexplored.

- Well-defined clinical scoring: We used standardized scoring systems (Clinical Severity Score [CSS] and Respiratory Distress Assessment Instrument [RDAI]) to objectively assess treatment response.

- Contextualizing within Vietnamese healthcare: This study provides region-specific data from a Vietnamese pediatric population, contributing valuable evidence from an underrepresented demographic in global bronchiolitis research.

We believe our findings will help refine clinical decision-making regarding the use of hypertonic saline, particularly for mild-to-moderate bronchiolitis cases in hospitalized infants. We will reinforce this contribution in the Discussion section, highlighting how our study fits within the broader debate.

We hope these clarifications satisfy the reviewer’s concerns and strengthen the manuscript. Thank you again for the valuable feedback.

2 Revision 1

4 comments · 17 Mar 2025 – 2 Jun 2025

Referee 2 Reviewer

ACCEPT 17 Mar 2025

Hello dear Editor-in-Chief
The authors addressed all comments, and the manuscript is acceptable right now.
Noted with thanks

Referee 4 Reviewer

ACCEPT 26 May 2025

Hi
Considering the extensive revisions that the authors made to the article and the responses they gave to the objections of the respected reviewers, as well as the limitations of conducting a single-center study and comparison with the control group, the above article is acceptable.

Associate Editor

ACCEPT 30 May 2025

The authors of the article have generally addressed the reviewers' comments, and the necessary revisions have been made to the manuscript. Some limitations of the study, such as its single-center design, still remain. Moreover, the global outbreak of the COVID-19 virus in recent years also affects the study's findings. Nevertheless, considering the aforementioned points, the article is acceptable.

Editor-in-Chief

ACCEPT 2 Jun 2025

My decision about this manuscript is to accept it.