BMJ Paediatrics Open

Isotonic saline for children with bronchiolitis: a study protocol for a Randomized Controlled Non-inferiority Trial

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2023-002273
Article Type:	Protocol
Date Submitted by the Author:	15-Sep-2023
Complete List of Authors:	Schmidt, Marika; Rigshospitalet, Department of pediatrics; Slagelse Hospital, Department of pediatrics Daugberg , Rie ; Slagelse Hospital, Department of pediatrics Nygaard, Ulrikka; Rigshospitalet, Department of pediatrics Nielsen , Xiaohui; Zealand University Hospital Koge, Department of Clinical Microbiology Chawes, Bo; Herlev Hospital, Department of pediatrics Rytter, Maren ; Slagelse Hospital, Department of pediatrics Schoos, Ann-Marie; COPSAC,
Keywords:	Virology, Infant, Health services research

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Isotonic saline for children with bronchiolitis: a study protocol for a Randomized Controlled Non-inferiority Trial

Authors: Marika Nathalie Schmidt, M.D.[1], Rie Daugberg, M.D.[1], Ulrikka Nygaard M.D., Ph.D.[2], M.D., Xiaohui Chen Nielsen, M.D., Ph.D.[3], Bo Chawes M.D., Ph.D., D.M.Sc.[4+5], Maren Rytter*, M.D., Ph.D. [1], Ann-Marie Schoos*, M.D., Ph.D.[1+5]

*Shared senior authorship

Affiliations:
[1] Department of Pediatrics, Slagelse Hospital, Slagelse
[2] Department of Pediatrics, Rigshospitalet, Copenhagen
[3] Department of Clinical Microbiology, Zealand University Hospital, Koege
[4] Department of Pediatrics, Herlev Hospital, Herlev
[5] COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

Correspodence:
Associate Professor Ann-Marie Malby Schoos, MD, PhD
E-mail: ann-marie.schoos@dbac.com
Website: www.copsac.com

Article type: Protocol

Word count: 2473

Tables: 1

Figures: 1

Online Repository: yes

Abbreviations:

RSV	Respiratory Syncytial Virus
ICU	Intensive Care Unit
SAE	Serious Adverse events
DSMB	Data Safety and Monitoring Board
GCP	Good Clinical Practice
HR-QoL	Health-Related Quality of Life
FLACC	Face, Leg, Activity, Cry, and Consolability

Abstract

Introduction

Bronchiolitis is one of the most common reasons for hospital admissions in early childhood. As supportive treatment, some treatment guidelines suggest using nasal drops of isotonic saline to facilitate clearance of mucus from the airways. In addition, most pediatric departments in Denmark use nebulized isotonic saline for the same purpose, which can mainly be administered as part of inpatient care. However, no studies have ever directly tested the effect of saline in children with bronchiolitis.

Methods and analysis

The study is an investigator-initiated, multicenter, open label, randomized, controlled non-inferiority trial, and will be performed at six pediatric departments in Eastern Denmark. We plan to include 300 children aged 0-12 months admitted to hospital with bronchiolitis. Participating children are randomized 1:1:1 to either nebulized isotonic saline, nose drops with isotonic saline, or no isotonic saline therapy. All other treatment will be given according to standard guidelines.
The primary outcome is duration of hospitalization, analyzed according to intention-to-treat analysis using logistic regression. By including at least 249 children, we can prove non-inferiority with a limit of 12 hours admission, alpha 2.5% and a power of 80%. Other outcomes evaluated include symptom severity, ability to feed, need for respiratory support, and transfer to intensive care unit.

Ethics and dissemination

This study may inform current practice for supportive treatment of children with bronchiolitis. First, if isotonic saline is found to be helpful, it may be implemented into global guidelines. If no effect of saline is found, we should stop spending resources on an ineffective treatment. Second, if saline is effective, but nose drops are non-inferior to nebulization, it may reduce the workload of nurses, and possibly duration of hospitalization, because the treatment can be delivered by the parents at home.

Trial Registration: The study has been registered at ClinicalTrials.gov (NCT05902702)

Introduction

Worldwide bronchiolitis is among the primary reasons for hospitalizations of children during their first year of life. In Denmark and most high-income countries it is one of the most important reasons for otherwise healthy children to require respiratory support and admission to intensive care unit (ICU) [1].

Bronchiolitis is a lower respiratory tract infection in infants and young children, and can present with nasal discharge, upper airway obstruction, respiratory distress, apnea, and difficulties feeding. It is almost always caused by a viral pathogen, the most prominent being respiratory syncytial virus (RSV) [2], but other pathogens, like human metapneumovirus may cause similar symptoms.

In Denmark, approximately 3% of all children less than one year old are admitted to the hospital due to bronchiolitis [3], and accordingly, the disease exerts a significant pressure on pediatric departments as well as the affected families. For the hospitals, children admitted with bronchiolitis stresses pediatric acute-care capacity in the winter months, and for society, the economic burden is considerable.

Although pediatricians have treated children with bronchiolitis for generations, and despite the severity of the symptoms and high burden of disease, we still have limited evidence-based specific treatment to offer these children. Treatment is generally supportive and may include clearance of mucus from the upper airway, since young infants are nasal breathers, and nasal secretions may contribute to respiratory distress [4-8]. In Danish pediatric departments, it has become common practice to use nebulized isotonic saline aiming to improve mucus clearance, despite the lack of evidence for its effect. This practice is largely based on theoretical advantages of saline in diluting mucus, on clinical experience, and supported indirectly by evidence from studies using nebulized saline as placebo when testing other treatments [9]. Isotonic saline is generally considered harmless and noninvasive. However, some children find the treatment unpleasant and react by crying, which may potentially worsen respiratory distress. The treatment is nebulized using pressurized air and therefore mainly administered as inpatient care. A simpler treatment is isotonic saline administered as nose drops, which may serve the same purpose, and limited evidence suggest that this may assist in clearing mucus from the airways [10]. This can also be administered at home by the child's parents, potentially reducing the need for hospital admissions. Even if inpatient care is required for other reasons, involving parents in the treatment with saline nose drops may reduce the workload on the nurses, and empower parents to manage their child's illness, as well as similar symptoms in the future.

Implementing effective, evidence-based, and family-friendly treatment for bronchiolitis is an important aspect of securing acute-care capacity. If we can minimize the use of ineffective treatments, and shorten the time children spend in the hospital, we can improve acute-care capacity and reduce the workload on nurses and reduce stress on families.

Objective
The trial aims to determine whether not using isotonic saline as part of supportive treatment of children with bronchiolitis is non-inferior to both nebulized saline and nose drops with isotonic saline in terms of duration of hospitalization.
Furthermore, the trial will investigate the current epidemiology of viral pathogens causing bronchiolitis in children in Denmark and assess whether children infected with specific pathogens might benefit from treatment with isotonic saline. The cohort will be followed up five years after inclusion, to explore predictors of later development of respiratory disease among children admitted with bronchiolitis.

Methods and analysis
This study is an investigator-initiated, multicenter, open label, three-arm randomized, controlled non-inferiority trial. Children, who meet the inclusion criteria (*Table 1*), will be asked to participate in the study.

Participants, intervention, and outcomes
Study setting: The study will be conducted at six pediatric departments in Eastern Denmark: Slagelse Hospital, Holbæk Hospital, Zealand University Hospital Roskilde, Copenhagen University Hospital Hvidovre, Copenhagen University Hospital Herlev, and Nykøbing Falster Hospital.

Eligibility criteria: The inclusion and exclusion criteria are listed in *Table 1*.
The exclusion criteria aim to minimize the risk of contaminating the population with other lung issues such as congenital lung diseases.

Randomization: Randomization is computerized using a web-based randomization module in REDCap. The web-based randomization generates randomization sequences with changing block sizes unknown to the investigators. Randomization will be conducted by the nurse caring for the patient.

Blinding: Due to the nature of the experimental intervention, no blinding can be performed among staff, parents or participating children. The outcome assessor investigating the primary outcome will be blinded.

Interventions: Participating children are randomized 1:1:1 to either nebulized isotonic saline, nose drops with isotonic saline, or no isotonic saline therapy. Nebulized saline is administered by a nebulization mask, supplied with pressurized air. Nose drops are administered first by the nurse, later by the parents. Both saline treatments are given every 3 hours. In case the treatments are needed more or less frequently, they will be administered accordingly. The frequency will be noted in the child's chart and accounted for when outcomes are reported. The treatment continues until the attending clinician assesses that it is no longer necessary. All other treatments are given according to standard guidelines, including suctioning of the upper airways as needed. Participating children will have a sample from the upper airways collected and tested for a panel of common viral

pathogens (Qiagen), and the remaining sample material will be stored in a biobank for later multi-omics analyses to investigate different endotypes of bronchiolitis and their association with later respiratory disease and underlying mechanisms.

Outcomes: The primary outcome is duration of hospitalization. Secondary outcomes are need for respiratory support with nasal continuous positive airway pressure or high-flow oxygen therapy, and requirement of fluid supplements (either by nasogastric tube or intravenous).
Exploratory outcomes include: (1) need for oxygen therapy (2) readmission after discharge, (3) clinician-initiated switch to the opposite treatment from the one they were randomized to, (4) highest pCO_2 measured (5) respiratory severity score with heart rate (Online repository) [11], (6) health-related quality of life (HR-QoL) (Online repository)[12], (7) visible distress in the child during delivery of treatment (or every three hours if randomized to no saline) using the Face, Leg, Activity, Cry, and Consolability (FLACC) scale [13,14], (8) parents' satisfaction with the given treatment using a Likert scale. This information will be collected by an online questionnaire send to the parents one month after admission, where parents will also be asked about the child's symptoms and the parent's experience with the hospitalization and the treatments offered, including a HR-QoL questionnaire. We will also check hospital files for any readmissions since the discharge.

Participant timeline and follow-up: Recruitment of participants will start in January 2024 and data collection is expected to last for 1.5 years. After the one-month follow up, children will be followed as an observational cohort to investigate the longer-term prognosis after admission with bronchiolitis. The children will be followed annually for 3 years by online questionnaires on respiratory symptoms, and by collecting data from hospital files regarding respiratory and infectious illness, and development of asthma and other chronic diseases (**Figure 1**).

Recruitment: Children will only be included if both parents provide oral and written informed consent. The parents will be informed that they can withdraw their consent without explanation at any time.

Risk and discomforts: Saline nose drops as well as nebulized saline may cause mild discomfort to some children during administration. However, it may also be a relief to have the airways cleared. Having a sample collected from the upper airways for analysis of viral pathogens may also cause mild discomfort. We will use material collected during suctioning of the upper airways, which is normally performed during admission, and thereby not causing any extra discomfort for the child. Nebulized saline and saline nose drops are also being carried out as standard of care to admitted children with bronchiolitis.

Safety and adverse events: An independent data safety and monitoring board (DSMB) will be established, consisting of an independent statistician and a physician. When half of the expected children are included in the study, the DSMB will receive blinded information about severe adverse events (SAE), defined as death, intubation, or transfer to semi-intensive care unit or intensive care

unit. An excess number of SAEs in either arm of the study will lead to the trial being paused until the committee has chosen whether the trial can continue or should be terminated.

Data collection and management

While interviewing the parents and examining the child upon admission, collected information will include baseline health data, medical history, current medications, family history of respiratory disease, smoking exposure, home environment, social activities, clinical presentation, and vital parameters.

Treating nurses will record the number of saline treatments given, respiratory score before and after saline treatment as well as distress at saline administration. In children randomized to no saline, respiratory score and distress will be recorded every three hours.

Data on other clinical findings, laboratory findings done as part of standard care, other treatments given, including oxygen, respiratory support, fluid therapy, transfer of patient to an ICU, adverse events, duration of admission, readmissions, new visits in emergency room and prescribed medicine will be collected from the child's medical record. All data will be entered in a REDCap database. Parents will complete an online questionnaire (*online repository*) one month after discharge in REDCap.

Respiratory samples will be analyzed using QIAstat-Dx Respiratory SARS-CoV-2 panel RP2.0 (QIAstat-Dx RP2.0) (QIAGEN, Hilden, Germany). This syndromic panel, using multiplex PCR technology, allows for the detection of 21 respiratory viruses and bacteria including SARS-CoV-2 (*Mycoplasma pneumoniae, Clamydophila pneumoniae, Bordetella pertussis,* Influenza A, Influenza A subtype H1N1/2009, Influenza A subtype H1, Influenza A subtype H3, Influenza B, Coronavirus 229 E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Adenovirus, Respiratory Syncytial Virus A/B, Human Metapneumovirus A/B, Rhinovirus/Enterovirus, and SARS-CoV-2 in a single run.

Data management and monitoring: Acquired data are stored in the secure REDCap system provided by Region Zealand. The data are entered electronically, both by researchers and by the parents.

Statistical analysis plan

Sample size determination: Among children admitted with bronchiolitis, the mean length of hospital stay is estimated to 32 hours (± 25) [15]. By including 249 children in total (83 in each arm), we can prove non-inferiority of no saline relative to nose drops or nebulized saline with a non-inferiority limit of 12 hours admission, alpha 2.5% and a power of 80%. We aim to include 300 children in total to account for dropouts.

Statistical analyses

Anonymized data will be analyzed in R statistics. Primary, secondary, exploratory and safety outcomes will be analyzed according to the principles in an intention-to-treat analysis. As a secondary analysis, we will also analyze all outcomes as 'per-protocol', i.e., only the randomized participants who have received the allocated treatment algorithm as defined in the protocol will be included. The primary outcome (duration of hospitalization) will be recorded as hours and comparing the mean hours of hospitalization between two study groups (no saline vs. nebulized saline, no saline vs. nasal irrigation, and nebulized saline vs. nasal irrigation) will be done using the Student's t-test or the non-parametric Wilcoxon-Mann-Whitney test in case the variable is not normally distributed. To compare all three groups, we will use the ANOVA test.
The investigation is analyzed as a non-inferiority study, which means that our aim is to prove that there is no clinically relevant difference between the two treatments according to the primary aim of the study.
Statistical significance for our non-inferiority analysis will be considered if the upper limit of a one-sided 97.5% CI excludes a difference that is more than the non-inferiority limit of the corresponding outcome. Statistical significance for our superiority analyses will therefore be considered if $P < 0.025$.

Ethics and dissemination

The trial will be conducted according to good clinical research practice (GCP) and the latest Declaration of Helsinki [16].
We consider the study safe, as the two experimental treatments are already regularly used in current practice. Also, the physician may change the treatment if this is determined to be best for the child, always assuring that the child gets the best treatment possible.

Publication: The results of the study, whether positive or negative, will be submitted for publication in an international peer-reviewed medical journal.

Research Ethics Approval

The trial protocol has been approved by the Regional Ethics Committee SJ-1023.

Discussion

Using saline for bronchiolitis represents one of many examples of an everyday treatment that has never been tested in clinical trials, and it is a continuous subject of debate in evidence-based medicine [17,18,19]. For bronchiolitis, previously tested specific treatments include bronchodilators [4], corticosteroids [5], antibiotics [6], and nebulized hypertonic saline [7] among others, none of which have proven effective. Accordingly, the treatment we currently offer is mainly supportive, securing respiration, oxygenation, nutrition, and hydration until recovery, and even for supportive treatment we have limited evidence for which is most helpful.

Isotonic saline nose drops are only mentioned sporadically in some international guidelines. The Royal Children's Hospital in Melbourne's practice guidelines suggest that "Saline drops may be used at time of feeding" [20], UpToDate suggest that "Saline nose drops and mechanical aspiration

of nares may help to relieve partial upper airway obstruction in infants and young children with respiratory distress or feeding difficulties" [21]. In contrast, the NICE guidelines [22] do not mention the use of saline nose drops at all.
The recent review by Dalziel et al. [23] recommends further evaluation of the benefit of suctioning and nasal saline drops. It is urgent to test our standard clinical practice with randomized, controlled trials, which will benefit both patients and caregivers, and improve the healthcare systems' prioritization of effective care.

This study may inform current practice for supportive treatment of children with bronchiolitis. If saline is found to be helpful, it may be implemented into global guidelines as standard clinical practice. If no effect of saline is found, we may stop spending resources on an ineffective treatment. Also, if saline is effective, but nose drops are non-inferior to nebulization, it may reduce the workload of nurses, and possibly duration of hospitalization, because the treatment can be delivered by the parents at home.

Authors contributions

The guarantors of the study are AMS and MJR who have been responsible for the integrity of the work as a whole, from conception and design to writing the manuscript. MNS was responsible for writing the first draft of the manuscript. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript. All co-authors have provided important intellectual input and approval of the final version of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Funding statement

This work was supported by "Den Lokale Forskningspulje for Næstved, Slagelse og Ringsted Sygehuse" - grant number A1317 and by "Region Sjællands Sundhedsvidenskabelige forskningsfond" - grant number R37-A1518

Competing interest statement

The authors declare no potential, perceived, or real conflict of interest regarding the content of this manuscript.

References

1. Jensen A, A F Simões E, Bohn Christiansen C, et al. Respiratory syncytial virus and influenza hospitalizations in Danish children 2010-2016. Vaccine 2021;39:4126–34.
2. Skjerven HO, Megremis S, Papadopoulos NG, et al. Virus Type and Genomic Load in Acute Bronchiolitis: Severity and Treatment Response With Inhaled Adrenaline. J Infect Dis 2016;213:915–21.
3. Johannesen CK, van Wijhe M, Tong S, et al. Age-Specific Estimates of Respiratory Syncytial Virus-Associated Hospitalizations in 6 European Countries: A Time Series Analysis. J Infect Dis 2022;226:S29–37.
4. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2014 Jun 17;2014(6):CD001266. doi: 10.1002/14651858.CD001266.pub4. PMID: 24937099; PMCID: PMC7055016.
5. Fernandes RM, Hartling L. Glucocorticoids for acute viral bronchiolitis in infants and young children. JAMA 2014;311:87–8.
6. Farley R, Spurling GKP, Eriksson L, et al. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 2014;10:CD005189.
7. Zhang L, Mendoza-Sassi RA, Wainwright C, et al. Nebulised hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2017;12:CD006458.
8. Kooiman L, Blankespoor F, Hofman R, Kamps A, Gorissen M, Vaessen-Verberne A, Heuts I, Bekhof J. High-flow oxygen therapy in moderate to severe bronchiolitis: a randomised controlled trial. Arch Dis Child. 2023 Jun;108(6):455-460. doi: 10.1136/archdischild-2022-324697. Epub 2023 Mar 20. PMID: 36941030.
9. House SA, Gadomski AM, Ralston SL. Evaluating the Placebo Status of Nebulized Normal Saline in Patients With Acute Viral Bronchiolitis: A Systematic Review and Meta-analysis. JAMA Pediatr 2020;174:250–9.
10. Schreiber S, Ronfani L, Ghirardo S, et al. Nasal irrigation with saline solution significantly improves oxygen saturation in infants with bronchiolitis. Acta Paediatr 2016;105:292–6.
11. A simple respiratory severity score that may be used in evaluation of acute respiratory infection - PubMed [Internet]. [cited 2022 Nov 17].Available from: https://pubmed-ncbi-nlm-nih-gov.ez-sus.statsbiblioteket.dk:12048/26868120/
12. Díez-Gandía E, Gómez-Álvarez C, López-Lacort M, et al. The impact of childhood RSV infection on children's and parents' quality of life: a prospective multicenter study in Spain. BMC Infect Dis 2021;21:924.
13. Kawade A, Dayma G, Apte A, Roy S, Gondhali A, Juvekar S, Bavdekar A. Assessment of perceived distress due to nasopharyngeal swab collection in healthy Indian infants participating in a clinical trial. Paediatr Neonatal Pain. 2021 Dec 26;3(4):170-175. doi: 10.1002/pne2.12068. PMID: 35548556; PMCID: PMC8975197.
14. Babl FE, Crellin D, Cheng J, Sullivan TP, O'Sullivan R, Hutchinson A. The use of the faces, legs, activity, cry and consolability scale to assess procedural pain and distress in young children. Pediatr Emerg Care. 2012 Dec;28(12):1281-96. doi: 10.1097/PEC.0b013e3182767d66. PMID: 23187981.

15. Chung A, Reeves RM, Nair H, et al. Hospital Admission Trends for Bronchiolitis in Scotland, 2001-2016: A National Retrospective Observational Study. J Infect Dis 2020;222:S592–8.
16. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects - PubMed [Internet]. [cited 2022 Nov 17].Available from: https://pubmed-ncbi-nlm-nih-gov.ez-sus.statsbiblioteket.dk:12048/24141714/
17. Mathew JL. Does Normal Saline Have Clinical Effects in Infants with Bronchiolitis?: Evidence-based Medicine Viewpoint. Indian Pediatr. 2020 Mar 15;57(3):254-257. PMID: 32198866.
18. Ren CL. Inhaled Isotonic Saline for Bronchiolitis. *JAMA Pediatr.* 2020;174(9):913. doi:10.1001/jamapediatrics.2020.1343
19. Gupta S. Does Normal Saline Have Clinical Effects in Infants with Bronchiolitis?: Pediatric Pulmonologist's Viewpoint. Indian Pediatr. 2020 Mar 15;57(3):257. PMID: 32198867.
20. Clinical Practice Guidelines : Clinical Practice Guidelines [Internet]. [cited 2022 Nov 15].Available from: https://www.rch.org.au/clinicalguide/#tab-B
21. UpToDate. Bronchiolitis in infants and children: Treatment, outcome, and prevention - UpToDate [Internet]. [cited 2022 Nov 17]. Available from: https://www.uptodate.com/contents/bronchiolitis-in-infants-and-children-treatment-outcome-and-prevention?search=brochilitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
22. www.nice.org.uk/guidance/ng9
23. Dalziel SR, Haskell L, O'Brien S, et al. Bronchiolitis. Lancet 2022;400:392–406.

Table 1

Overview of the inclusion and exclusion criteria for saline treatment

Inclusion criteria:

- Hospitalization due to symptoms of bronchiolitis*.
- Age 0-12 months.
- Parents provide informed consent for participation.

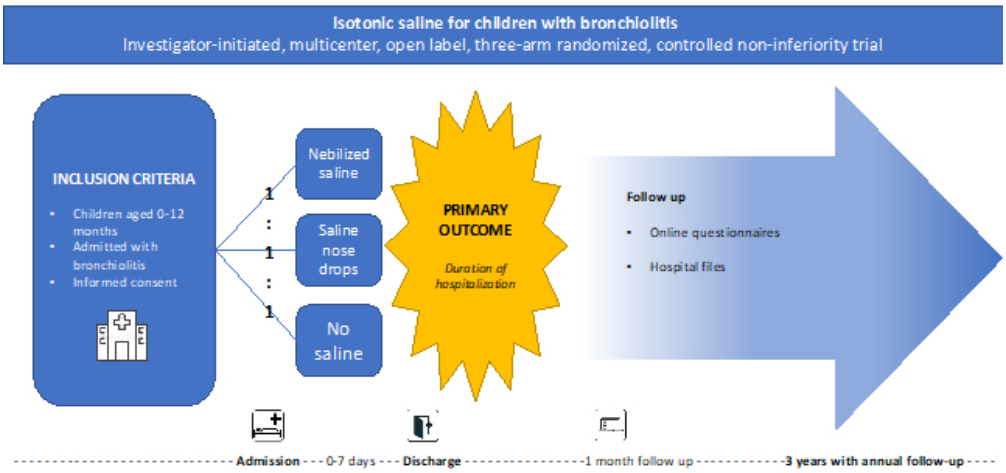
Exclusion criteria:

- Children with cystic fibrosis or other serious congenital chronic lung diseases.
- Children in whom treatment with short-acting beta-2 agonist is initiated (as this is delivered in nebulized isotonic saline).
- Children who, after inclusion, are found to have a different acute lung disease than bronchiolitis.

*Runny nose, dry and persistent cough, labored breathing (tachypnea, retractions, nasal flaring) grunting, cyanosis or apnea, wheezing or crackles on auscultation, O_2 saturations below 92 %, difficulties feeding.

Table 1

230x325mm (130 x 130 DPI)



Study Outline

429x241mm (38 x 38 DPI)

Appendices

A1: QUESTIONNAIRES USED FOR THE STUDY

(English version – will be translated to Danish)

A1.1: HR-QoL

CHILD'S SYMPTOMS
ANSWER THE FOLLOWING QUESTIONS ABOUT YOUR CHILD'S ILLNESS

1. During the last week, how many days has your child presented the following symptoms?

	0	1/2	1	2	3	4	5	6	7
Cough									
Dyspnea (fast breathing, intercostal retractions…)									
Wheezing									
Cyanosis (Blueness in face/lips)									
Less appetite than usual									
Full days without eating									
Fever									

2. In comparison with the previous week, your child's symptoms this week have been: much worst, somewhat worse, the same, somewhat better, much better.

CONCERN ABOUT CHILD'S SYMPTOMS

3. How worried have you felt about the following symptoms:
* If in question 1 you marked "0 days", please go directly to question 6.

	Not worried	Slightly worried	Quite worried	Very worried
Cough				
Dyspnea (fast breathing, intercostal retractions…)				
Wheezing				
Cyanosis (Blueness in face/lips)				
Less appetite than usual				
Full days without eating				
Fever				

4. If your child has presented fever, what was the highest temperature that he/she presented? (Select from 37 to 42ºC)

5. Overall, during the last week, how worried have you felt about your child's disease? Not worried, slightly worried, quite worried, very worried.

6. In comparison to the previous week, your concern about your child's symptoms has been: much worst, somewhat worse, the same, somewhat better, much better.

CHILD'S BEHAVIOR DURING THE ILLNESS

The following questions are about your child's behavior during the illness.
Please select the box of the answer that best applies to your son/daughter's case.
7. During the last week, your child:

	Never	Sometimes	Often	Always
Has slept more than usual				
Has slept less than usual				
Has cried more than usual				
Has been more irritable				
Has had less desire to play				
Has been exhausted				
Has been less attentive				
Has needed more comfort				

8. In comparison to the previous week, your child's behavior has been: much worst, somewhat worse, the same, somewhat better, much better.

CONCERN ABOUT CHILD'S ILLNESS

The following questions are about what you felt as a father/mother about your child's disease.
Please select the box of the answer that best applies to your case.

9. During the last week, have you had the following feelings concerning your child's illness?

	No at all	A little bit	A lot	A great deal
Sadness to see my child being ill				
Impotence				
Mental exhaustion				
Physical exhaustion				
Guiltiness				
Fed up with the situation				

10. In comparison to the previous week, your emotions about your son/daughter's illness this week have been: much worst, somewhat worse, the same, somewhat better, much better.

YOUR DAILY ACTIVITIES DURING YOUR CHILD'S DISEASE

How much has your child's illness interfered in your daily activities?
Please select the box of the answer that best applies to your case.

11. During the last week and concerning your child's disease:

	0	1/2	1	2	3	4	5	6	7
How many nights did the illness disrupted your sleep?									
How many days did you have to dedicate exclusively to your child?									
How many days did you have to ask for help to someone else (parents, friends, neighbors…)?									
How many days could not he/she attend nursery school, or you could not leave him/her home with a babysitter?									

12. During the last week and concerning your child's disease:

	No at all	A little bit	A lot	A great deal
Have you lost sleep hours?				
Your child's illness limited your leisure time?				
Your child's illness limited the time for doing the groceries				
Your child illness limited the time for doing house chores				

13. Who has completed this questionnaire? Mother, Father or other.

A1.2: Satisfaction with treatment:

1: Overall, how happy were you with the treatment given in hospital?

1	2	3	4	5	6	7	8	9	10

Very unsatisfied Neutral Verry satisfied

2: If your child was given saline during treatment:

A: did your child react with crying or distress during administration of saline?

1	2	3	4	5	6	7	8	9	10

Strongly disagree Neutral Strongly Agree

B: Did you find that saline helped your child to clear the airways:

1	2	3	4	5	6	7	8	9	10

Strongly disagree Neutral Strongly Agree

3: After discharge, did you administrate saline to your child at home?

Yes	
No	

A2 Respiratory severity scoring with heart rate

Score	**Respiratory rate**	**Wheeze**	**Heart rate[a]**	SpOb2	**Accessory muscle use**
0	<30	None	<150	>95	None
1	30–45	End-expiratory only	151–160	94–95	Mild intercostal retractions
2	46–60	Entire expiration and inspiration with stethoscope	161–170	90–93	Moderate retractions
3	>60	Entire expiration and inspiration without stethoscope	>170	<90	Moderate retractions + head bobbing or tracheal tugging

[a]RSS-HR = respiratory rate + wheeze + heart rate + accessory muscle use
[b]RSS-SO = respiratory rate + wheeze + SpO_2 + accessory muscle use

BMJ Paediatrics Open

Normal saline for children with bronchiolitis: Study protocol for a Randomized Controlled Non-inferiority Trial

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2023-002273.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Nov-2023
Complete List of Authors:	Schmidt, Marika; Rigshospitalet, Department of pediatrics; Slagelse Hospital, Department of pediatrics Daugberg , Rie ; Slagelse Hospital, Department of pediatrics Nygaard, Ulrikka; Rigshospitalet, Department of pediatrics Nielsen , Xiaohui; Zealand University Hospital Koge, Department of Clinical Microbiology Chawes, Bo; Herlev Hospital, Department of pediatrics Rytter, Maren ; Slagelse Hospital, Department of pediatrics Schoos, Ann-Marie; COPSAC,
Keywords:	Virology, Infant, Health services research

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Normal saline for children with bronchiolitis: Study protocol for a Randomized Controlled Non-inferiority Trial

Authors: Marika Nathalie Schmidt, M.D.[1], Rie Daugberg, M.D.[1], Ulrikka Nygaard M.D., Ph.D.[2], M.D., Xiaohui Chen Nielsen, M.D., Ph.D.[3], Bo Lung Krogsgaard Chawes M.D., Ph.D., D.M.Sc.[4+5], Maren Heilskov Rytter*, M.D., Ph.D. [1], Ann-Marie Malby Schoos*, M.D., Ph.D.[1+5]

*Shared senior authorship

Affiliations:
[1] Department of Pediatrics, Slagelse Hospital, Slagelse
[2] Department of Pediatrics, Rigshospitalet, Copenhagen
[3] Department of Clinical Microbiology, Zealand University Hospital, Koege
[4] Department of Pediatrics, Herlev Hospital, Herlev
[5] COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

Correspodence:
Associate Professor Ann-Marie Malby Schoos, MD, PhD
E-mail: ann-marie.schoos@dbac.dk
Website: www.copsac.com

Article type: Protocol

Word count: 2603

Tables: 1

Figures: 1

Supplemental Material Online: yes

Abbreviations:

RSV	Respiratory Syncytial Virus
ICU	Intensive Care Unit
SAE	Serious Adverse events
DSMB	Data Safety and Monitoring Board
GCP	Good Clinical Practice
HR-QoL	Health-Related Quality of Life
FLACC	Face, Leg, Activity, Cry, and Consolability

Abstract

Introduction

Bronchiolitis is one of the most common reasons for hospital admissions in early childhood. As supportive treatment, some treatment guidelines suggest using nasal irrigation with normal saline (NS) to facilitate clearance of mucus from the airways. In addition, most pediatric departments in Denmark use nebulized NS for the same purpose, which can mainly be administered as inpatient care. However, no studies have ever directly tested the effect of saline in children with bronchiolitis.

Methods and analysis

The study is an investigator-initiated, multicenter, open label, randomized, controlled non-inferiority trial, and will be performed at six pediatric departments in eastern Denmark. We plan to include 300 children aged 0-12 months admitted to hospital with bronchiolitis. Participating children are randomized 1:1:1 to either nebulized NS, nasal irrigation with NS, or no saline therapy. All other treatment will be given according to standard guidelines.

The primary outcome is duration of hospitalization, analyzed according to intention-to-treat analysis using linear regression and Cox regression analysis. By including at least 249 children, we can prove non-inferiority with a limit of 12 hours admission, alpha 2.5% and a power of 80%. Secondary outcomes are need for respiratory support with nasal continuous positive airway pressure or high-flow oxygen therapy, and requirement of fluid supplements (either by nasogastric tube or intravenous).

Ethics and dissemination

This study may inform current practice for supportive treatment of children with bronchiolitis. First, if NS is found to be helpful, it may be implemented into global guidelines. If no effect of NS is found, we can stop spending resources on an ineffective treatment. Second, if NS is effective, but nasal irrigation is non-inferior to nebulization, it may reduce the workload of nurses, and possibly duration of hospitalization, because the treatment can be delivered by the parents at home.

Trial Registration: The study has been registered at ClinicalTrials.gov (NCT05902702)

KEY MESSAGES

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Bronchiolitis is among the primary reasons for hospitalizations of children during their first year of life.
- Nebulized normal saline is used widely to assist with clearing of mucus from the airways as part of the supportive treatment of bronchiolitis, with no direct evidence of efficacy.

WHAT THIS STUDY HOPES TO ADD

- To investigate whether normal saline administered as either nebulization or nasal irrigation is helpful in the management of bronchiolitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- If normal saline is found to be helpful, its use may be recommended in treatment guidelines. If no effect is found, we may stop spending resources on an ineffective treatment. If normal saline is effective, but nasal irrigation is non-inferior to nebulization, it may reduce the workload of nurses, and empower parents to manage their child's illness themselves.

Introduction

Worldwide, bronchiolitis is among the primary reasons for hospitalizations of children during their first year of life. In Denmark and most high-income countries it is one of the most important reasons for otherwise healthy children to require respiratory support and admission to intensive care unit (ICU) [1].

Bronchiolitis is a lower respiratory tract infection in infants and young children, and can present with nasal discharge, upper airway obstruction, respiratory distress, apnea, and difficulties feeding. It is almost always caused by a viral pathogen, the most prominent being respiratory syncytial virus (RSV) [2], but other pathogens, like human metapneumovirus may cause similar symptoms.

In Denmark, approximately 3% of all children less than one year old are admitted to the hospital due to bronchiolitis [3], and accordingly, the disease exerts a substantial pressure on pediatric departments as well as the affected families. For the hospitals, children admitted with bronchiolitis stresses pediatric acute-care capacity in the winter months, and for society, the economic burden is considerable.

Although pediatricians have treated children with bronchiolitis for generations, and despite the severity of symptoms and high burden of disease, we still have limited evidence-based specific treatment to offer these children [4-8]. Even though passive immunization strategies against RSV may change the disease pattern in the future, many children with bronchiolitis are still likely to require admission to hospital, where treatment is generally supportive [9, 10]. This may include clearance of mucus from the upper airways, since young infants are nasal breathers, and nasal secretions may contribute to respiratory distress. In Danish pediatric departments, it has become common practice to use nebulized normal saline (NS, 0.9% NaCl) aiming to improve mucus clearance, despite lack of evidence for its effect. This practice is based on theoretical advantages of saline in diluting mucus, and on clinical experience. NS is generally considered harmless and noninvasive. However, some children find the treatment unpleasant and react by crying, which may potentially worsen respiratory distress. A secondary analysis of studies using nebulized NS as placebo when testing other treatments suggested that nebulized NS could improve symptoms of respiratory distress, compared to an oral placebo [11]. In contrast, another study suggested that nebulized NS could cause airway obstruction [12]. A quality improvement study found that de-implementing the use of nebulized NS did not increase length of hospital stay for children with bronchiolitis [13]. The main limitation of these studies is the heterogeneity of the methodology which hinders comparison of the results. Further, they only report short-term physiologic measures, and not clinically relevant endpoints like duration of hospitalization or escalation of treatment.
NS is nebulized using pressurized air and can therefore mainly be administered as inpatient care. A simpler treatment is NS administered as nasal irrigation, which may serve the same purpose, and limited evidence suggest that this may assist in clearing mucus from the airways [14]. This can also be administered at home by the child's parents, potentially reducing the need for hospital admissions. Even if inpatient care is required for other reasons, involving parents in the treatment

with NS as nasal irrigation may reduce the workload on the nurses and empower parents to manage their child's illness, as well as similar symptoms in the future.

Implementing effective, evidence-based, and family-friendly treatment for bronchiolitis is an important aspect of securing acute-care capacity. If we can minimize the use of ineffective treatments, and shorten the time children spend in the hospital, we can improve acute-care capacity and reduce the workload on nurses and reduce stress on families.

Objective

The trial aims to determine whether not using NS as part of supportive treatment of children admitted with bronchiolitis is non-inferior to both nebulized NS and nasal irrigation with NS in terms of duration of hospitalization.

The study will also investigate the current epidemiology of viral pathogens causing bronchiolitis in children in Denmark and assess whether children infected with specific pathogens might benefit from treatment with NS. The cohort will be followed up five years after inclusion, to explore predictors of later development of respiratory disease among children admitted with bronchiolitis.

Methods and analysis

This study is an investigator-initiated, multicenter, open label, three-arm randomized, controlled non-inferiority trial. Children, who meet the inclusion criteria (*Table 1*), will be asked to participate in the study.

Participants, intervention, and outcomes

Study setting: The study will be conducted at six pediatric departments in Eastern Denmark: Slagelse Hospital, Holbæk Hospital, Zealand University Hospital Roskilde, Copenhagen University Hospital Hvidovre, Copenhagen University Hospital Herlev, and Nykøbing Falster Hospital.

Eligibility criteria: The inclusion and exclusion criteria are listed in *Table 1*. The child is preferably included immediately after admission, but may also be included later, for example if admitted at night and no saline treatment has been started yet.

The exclusion criteria aim to minimize the risk of contaminating the population with other lung issues such as congenital lung diseases. Children with any disease severity may be included, however, children who require respiratory support with nasal continuous positive airway pressure (N-CPAP) or high-flow oxygen therapy (HFOT) right from admission start will be excluded because this makes delivery of nebulized NS difficult. For children admitted with bronchiolitis who are not included in the study we will record the age, sex, and the reason for non-inclusion.

Randomization: Randomization is computerized using a web-based randomization module. The web-based randomization generates randomization sequences with changing block sizes unknown to the investigators. Randomization will be conducted by the nurse or doctor caring for the patient, in collaboration with the study coordinator. At randomization, children will be stratified according to whether they were born prematurely or not.

Table 1

Overview of the inclusion and exclusion criteria for saline treatment

Inclusion Criteria	Exclusion criteria
Hospitalization due to symptoms of bronchiolitis*	Children with cystic fibrosis or other serious congenital chronic lung diseases
Age 0-12 months	Children in whom treatment with short-acting beta-2 agonist is initiated (as this is delivered in nebulized isotonic saline)
Parents provide informed consent for participation	Children who, after inclusion, are found to have a different acute lung disease than bronchiolitis
	Children who, right at admission, need respiratory support in form of HFOT and CPAP

**Runny nose, dry and persistent cough, labored breathing (tachypnea, retractions, nasal flaring) grunting, cyanosis or apnea, wheezing or crackles on auscultation, O_2 saturations below 92 %, difficulties feeding.*

Blinding: Due to the nature of the experimental intervention, no blinding can be performed among staff, parents, or participating children. The outcome assessor investigating the primary outcome will be blinded.

Interventions: Participating children are randomized 1:1:1 to either nebulized NS, nasal irrigation with NS, or no saline therapy. Nebulized NS is administered by a nebulization mask, supplied with pressurized air. Nasal irrigation with NS is administered first by the nurse, later by the parents. Both NS treatments are given every three hours. In case the treatments are needed more or less frequently, they will be administered accordingly. The frequency will be noted in the child's chart and accounted for when outcomes are reported. The treatment continues until the attending clinician assesses that it is no longer necessary. All other treatments are given according to standard guidelines, including suctioning of the upper airways as needed. Participating children will have a sample from the upper airways collected and tested for a panel of common viral pathogens (Qiagen), and the remaining sample material will be stored in a biobank for later multi-omics analyses to investigate different endotypes of bronchiolitis and their association with later respiratory disease and underlying mechanisms.

Outcomes: The primary outcome is duration of hospitalization. Duration of hospitalization is defined as number hours from admission until a doctor has evaluated that the child is ready for discharge.

Secondary outcomes are need for respiratory support with NCPAP or HFOT, and requirement of fluid supplements (either by nasogastric tube or intravenous).

Exploratory outcomes include: (1) need for oxygen therapy according to local guidelines (usually oxygen saturation <90%) and doctor's discretion (2) readmission after discharge, (3) clinician-initiated switch to a different treatment from the one they were randomized to, (4) highest pCO_2 measured (5) respiratory severity score with heart rate, measured after treatment or every three hours if randomized to no saline treatment [15] (supplementary file *A2*), (6) visible distress in the child during delivery of treatment (or every three hours if randomized to no saline treatment) using the Face, Leg, Activity, Cry, and Consolability (FLACC) scale [17,18], (7) health-related quality of life (HR-QoL) [16] (supplementary file *A1.1*), (8) parents' satisfaction with the given treatment using a Likert scale (supplementary file *A1.2*).

Participant timeline and follow-up: Recruitment of participants will start January 1st, 2024, and recruitment is expected to last for one and a half year through two seasons of bronchiolitis. After the one-month follow up, children will be followed as an observational cohort to investigate the longer-term prognosis after admission with bronchiolitis. The children will be followed annually for five years by online questionnaires on respiratory symptoms, and by collecting data from hospital files regarding respiratory and infectious illness, and development of asthma and other chronic diseases (**Figure 1**).

Recruitment: Children will only be included if both parents provide oral and written informed consent. The parents will be informed that they can withdraw their consent without explanation at any time.

Risk and discomforts: Nasal irrigation with NS as well as nebulized NS may cause mild discomfort to some children during administration. However, it may also be a relief to have the airways cleared. Having a sample collected from the upper airways for analysis of viral pathogens may also cause mild discomfort. If possible, we will use material collected during suctioning of the upper airways, which is normally performed during admission, and thereby not causing any extra discomfort for the child. Nebulized NS and nasal irrigation with NS are already being carried out as standard of care to admitted children with bronchiolitis.

Safety and adverse events: An independent data safety and monitoring board (DSMB) will be established, consisting of an independent statistician and a physician. When half of the expected children are included in the study, the DSMB will receive blinded information about severe adverse events (SAE), defined as death, intubation, or transfer to semi-intensive care unit or intensive care unit. An excess number of SAEs in either arm of the study will lead to the trial being paused until the committee has chosen whether the trial can continue or should be terminated.

Data collection and management

While interviewing the parents and examining the child upon admission, information will be collected about symptoms and treatment given at home, baseline health data including feeding practice, medical history including factors related to pregnancy and birth, gestational age and neonatal course, comorbidities, medications, risk factors, including family history of respiratory disease and allergies, smoking exposure, home environment, socio-economic status, clinical presentation, and vital parameters.

Treating nurses will record the number of saline treatments given, respiratory score before and after saline treatment, as well as distress at saline administration. In children randomized to no saline, respiratory score and distress will be recorded every three hours.

Data collection will be standardized across sites using a standardized electronic patient record.

Data on other clinical findings, laboratory findings done as part of standard care, other treatments given, including oxygen, respiratory support, fluid therapy, transfer of patient to an ICU, adverse events, duration of admission, readmissions, new visits in emergency room, and prescribed medicine will be collected from the child's medical record. All data will be entered in a REDCap database. Parents will be asked to complete an online questionnaire one month after discharge in REDCap, asking about the child's symptoms and the parent's experience and satisfaction with the hospitalization and treatments offered, as well as HR-QoL.

Respiratory samples will be analyzed using QIAstat-Dx Respiratory SARS-CoV-2 panel RP2.0 (QIAstat-Dx RP2.0) (QIAGEN, Hilden, Germany). This syndromic panel, using multiplex PCR technology, allows for the detection of 21 respiratory viruses and bacteria including *Mycoplasma pneumoniae, Clamydophila pneumoniae, Bordetella pertussis,* Influenza A, Influenza A subtype H1N1/2009, Influenza A subtype H1, Influenza A subtype H3, Influenza B, Coronavirus 229 E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Adenovirus, Respiratory Syncytial Virus A/B, Human Metapneumovirus A/B, Rhinovirus/Enterovirus, and SARS-CoV-2 in a single run.

Data management and monitoring: Acquired data are entered and stored electronically in REDCap.

Statistical analysis plan

Sample size determination: Among children admitted with bronchiolitis, the mean duration of hospitalization is estimated to 32 hours (± 25) [19]. By including 249 children in total (83 in each arm), we can prove non-inferiority of no saline relative to nasal irrigation with NS or nebulized NS with a non-inferiority limit of 12 hours admission, alpha 2.5% and a power of 80%. We aim to include 300 children in total to account for dropouts.

Statistical analyses

Anonymized data will be analyzed in R statistics. Primary, secondary, exploratory and safety outcomes will be analyzed according to the principles in an intention-to-treat analysis. As a secondary analysis, we will also analyze all outcomes as 'per-protocol', i.e., only the randomized participants who have received the allocated treatment algorithm as defined in the protocol will be included.

The primary outcome (duration of hospitalization) will be recorded as hours. The three groups (no saline vs. nebulized NS, no saline vs. nasal irrigation with NS, and nebulized NS vs. nasal irrigation with NS) will be compared using linear regression and Cox regression analysis. The investigation is analyzed as a non-inferiority study, which means that our aim is to prove that there is no clinically relevant difference between the two treatments according to the primary aim of the study.

Secondary outcomes will be tested using logistic regression. Exploratory outcomes are both binary (1-3) and continuous (4-8) and will be analyzed with linear and logistic regression respectively.

Statistical significance for our non-inferiority analysis will be considered if the upper limit of a one-sided 97.5% CI excludes a difference that is more than the non-inferiority limit of the corresponding

outcome. Statistical significance for our superiority analyses will therefore be considered if $P < 0.025$.

Ethics and dissemination

The trial will be conducted according to good clinical research practice and the Declaration of Helsinki [20].

We consider the study safe, as the two experimental treatments are already regularly used in current practice. Also, the physician may change the treatment if this is determined to be best for the child, always assuring that the child gets the best treatment possible.

Publication: The results of the study, whether positive or negative, will be submitted for publication in an international peer-reviewed medical journal.

Research Ethics Approval

The trial protocol has been approved by the Ethics Committee of Region Zealand with ID: EMN-2023-00012.

Discussion

Using NS for bronchiolitis represents one of many examples of an everyday treatment that has never been tested in clinical trials, and it is a continuous subject of debate in evidence-based medicine [21,22,23]. For bronchiolitis, previously tested specific treatments include bronchodilators [4], corticosteroids [5], antibiotics [6], and nebulized hypertonic saline [7] among others, none of which have proven effective. Accordingly, the treatment we currently offer is mainly supportive, securing respiration, oxygenation, nutrition, and hydration until recovery, and even for supportive treatment we have limited evidence for which is most helpful.

Nasal irrigation with NS is mentioned sporadically in some international guidelines. The Royal Children's Hospital in Melbourne's practice guidelines suggest that "Saline drops may be used at time of feeding" [24], UpToDate suggest that "Saline nose drops and mechanical aspiration of nares may help to relieve partial upper airway obstruction in infants and young children with respiratory distress or feeding difficulties" [25]. In contrast, the NICE guidelines [26] do not mention the use of nasal irrigation with NS at all.

A recent review [27] recommends further evaluation of the benefit of suctioning and nasal irrigation with NS. It is urgent to test our standard clinical practice with randomized, controlled trials, which will benefit patients and caregivers and enable prioritization of effective care in healthcare systems.

This study may inform current practice for supportive treatment of children with bronchiolitis. If saline is found to be helpful, it may be implemented into global guidelines as standard clinical practice. If no effect of NS is found, we may stop spending resources on an ineffective treatment. Also, if NS is effective, but nasal irrigation is non-inferior to nebulization, it may reduce the workload of nurses, and possibly duration of hospitalization, because the treatment can be delivered by the parents at home.

Authors contributions

The guarantors of the study are AMS and MJR who have been responsible for the integrity of the work as a whole, from conception and design to writing the manuscript. MNS wrote the first draft of the manuscript. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript. All co-authors have provided important intellectual input, revised, and approved the final version of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Funding statement

This work was supported by "Den Lokale Forskningspulje for Næstved, Slagelse og Ringsted Sygehuse" - grant number A1317 and by "Region Sjællands Sundhedsvidenskabelige forskningsfond" - grant number R37-A1518

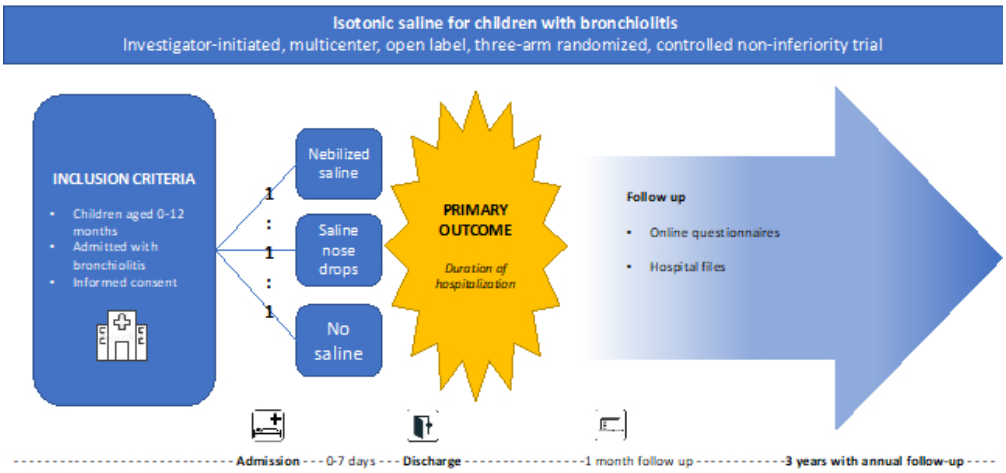
Competing interest statement

The authors declare no potential, perceived, or real conflict of interest regarding the content of this manuscript.

References

1. Jensen A, A F Simões E, Bohn Christiansen C, et al. Respiratory syncytial virus and influenza hospitalizations in Danish children 2010-2016. Vaccine 2021;39:4126–34.
2. Skjerven HO, Megremis S, Papadopoulos NG, et al. Virus Type and Genomic Load in Acute Bronchiolitis: Severity and Treatment Response With Inhaled Adrenaline. J Infect Dis 2016;213:915–21.
3. Johannesen CK, van Wijhe M, Tong S, et al. Age-Specific Estimates of Respiratory Syncytial Virus-Associated Hospitalizations in 6 European Countries: A Time Series Analysis. J Infect Dis 2022;226:S29–37.4. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2014 Jun 17;2014(6):CD001266. doi: 10.1002/14651858.CD001266.pub4. PMID: 24937099; PMCID: PMC7055016.
5. Fernandes RM, Hartling L. Glucocorticoids for acute viral bronchiolitis in infants and young children. JAMA 2014;311:87–8.
6. Farley R, Spurling GKP, Eriksson L, et al. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 2014;10:CD005189.
7. Zhang L, Mendoza-Sassi RA, Wainwright C, et al. Nebulised hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2017;12:CD006458.
8. Kooiman L, Blankespoor F, Hofman R, Kamps A, Gorissen M, Vaessen-Verberne A, Heuts I, Bekhof J. High-flow oxygen therapy in moderate to severe bronchiolitis: a randomised controlled trial. Arch Dis Child. 2023 Jun;108(6):455-460. doi: 10.1136/archdischild-2022-324697. Epub 2023 Mar 20. PMID: 36941030.
9. Verwey C, Madhi SA. Review and Update of Active and Passive Immunization Against Respiratory Syncytial Virus. BioDrugs. 2023 May;37(3):295-309. doi: 10.1007/s40259-023-00596-4. Epub 2023 Apr 25. PMID: 37097594; PMCID: PMC10127166.
10. Pukai G, Duke T. **Nebulised normal saline in moderate acute bronchiolitis and pneumonia in a low- to middle-income country: a randomised trial in Papua New Guinea.** Paediatr Int Child Health. 2020 Aug;40(3):171-176. doi: 10.1080/20469047.2020.1725338. Epub 2020 Feb 17. PMID: 32063157.
11. House SA, Gadomski AM, Ralston SL. Evaluating the Placebo Status of Nebulized Normal Saline in Patients With Acute Viral Bronchiolitis: A Systematic Review and Meta-analysis. JAMA Pediatr 2020;174:250–9.
12. Sautter M, Halvorsen T, Engan M, Clemm H, Bentsen MHL. **Electromagnetic inductance plethysmography to study airflow after nebulized saline in bronchiolitis.** Pediatr Pulmonol. 2020 Dec;55(12):3437-3442. doi: 10.1002/ppul.25058. Epub 2020 Sep 15. PMID: 32897652.
13. Hassan S, Gonzalez A, Demissie S, Morawakkoralage K, James P. **Nebulized Normal Saline Solution for Treatment of Bronchial Asthma Exacerbations and Bronchiolitis: Not Standard of Care.** Clin Pediatr (Phila). 2018 Nov;57(13):1582-1587. doi: 10.1177/0009922818796657. Epub 2018 Sep 6. PMID: 30188182.
14. Schreiber S, Ronfani L, Ghirardo S, et al. Nasal irrigation with saline solution significantly improves oxygen saturation in infants with bronchiolitis. Acta Paediatr 2016;105:292–6.

15. A simple respiratory severity score that may be used in evaluation of acute respiratory infection - PubMed [Internet]. [cited 2022 Nov 17].Available from: https://pubmed-ncbi-nlm-nih-gov.ez-sus.statsbiblioteket.dk:12048/26868120/
16. Díez-Gandía E, Gómez-Álvarez C, López-Lacort M, et al. The impact of childhood RSV infection on children's and parents' quality of life: a prospective multicenter study in Spain. BMC Infect Dis 2021;21:924.
17. Kawade A, Dayma G, Apte A, Roy S, Gondhali A, Juvekar S, Bavdekar A. Assessment of perceived distress due to nasopharyngeal swab collection in healthy Indian infants participating in a clinical trial. Paediatr Neonatal Pain. 2021 Dec 26;3(4):170-175. doi: 10.1002/pne2.12068. PMID: 35548556; PMCID: PMC8975197.
18. Babl FE, Crellin D, Cheng J, Sullivan TP, O'Sullivan R, Hutchinson A. The use of the faces, legs, activity, cry and consolability scale to assess procedural pain and distress in young children. Pediatr Emerg Care. 2012 Dec;28(12):1281-96. doi: 10.1097/PEC.0b013e3182767d66. PMID: 23187981.
19. Chung A, Reeves RM, Nair H, et al. Hospital Admission Trends for Bronchiolitis in Scotland, 2001-2016: A National Retrospective Observational Study. J Infect Dis 2020;222:S592–8.
20. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects - PubMed [Internet]. [cited 2022 Nov 17].Available from: https://pubmed-ncbi-nlm-nih-gov.ez-sus.statsbiblioteket.dk:12048/24141714/
21. Mathew JL. Does Normal Saline Have Clinical Effects in Infants with Bronchiolitis?: Evidence-based Medicine Viewpoint. Indian Pediatr. 2020 Mar 15;57(3):254-257. PMID: 32198866.
22. Ren CL. Inhaled Isotonic Saline for Bronchiolitis. *JAMA Pediatr.* 2020;174(9):913. doi:10.1001/jamapediatrics.2020.1343
23. Gupta S. Does Normal Saline Have Clinical Effects in Infants with Bronchiolitis?: Pediatric Pulmonologist's Viewpoint. Indian Pediatr. 2020 Mar 15;57(3):257. PMID: 32198867.
24. Clinical Practice Guidelines : Clinical Practice Guidelines [Internet]. [cited 2022 Nov 15].Available from: https://www.rch.org.au/clinicalguide/#tab-B
25. UpToDate. Bronchiolitis in infants and children: Treatment, outcome, and prevention - UpToDate [Internet]. [cited 2022 Nov 17]. Available from: https://www.uptodate.com/contents/bronchiolitis-in-infants-and-children-treatment-outcome-and-prevention?search=brochilitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
26. www.nice.org.uk/guidance/ng9
27. Dalziel SR, Haskell L, O'Brien S, et al. Bronchiolitis. Lancet 2022;400:392–406.



Study Outline

429x241mm (38 x 38 DPI)

Appendices

A1: QUESTIONNAIRES USED FOR THE STUDY

(English version – will be translated to Danish)

A1.1: HR-QoL

CHILD'S SYMPTOMS
ANSWER THE FOLLOWING QUESTIONS ABOUT YOUR CHILD'S ILLNESS

1. During the last week, how many days has your child presented the following symptoms?

	0	1/2	1	2	3	4	5	6	7
Cough									
Dyspnea (fast breathing, intercostal retractions…)									
Wheezing									
Cyanosis (Blueness in face/lips)									
Less appetite than usual									
Full days without eating									
Fever									

2. In comparison with the previous week, your child's symptoms this week have been: much worst, somewhat worse, the same, somewhat better, much better.

CONCERN ABOUT CHILD'S SYMPTOMS

3. How worried have you felt about the following symptoms:
* If in question 1 you marked "0 days", please go directly to question 6.

	Not worried	Slightly worried	Quite worried	Very worried
Cough				
Dyspnea (fast breathing, intercostal retractions…)				
Wheezing				
Cyanosis (Blueness in face/lips)				
Less appetite than usual				
Full days without eating				
Fever				

4. If your child has presented fever, what was the highest temperature that he/she presented? (Select from 37 to 42ºC)

5. Overall, during the last week, how worried have you felt about your child's disease? Not worried, slightly worried, quite worried, very worried.

6. In comparison to the previous week, your concern about your child's symptoms has been: much worst, somewhat worse, the same, somewhat better, much better.

CHILD'S BEHAVIOR DURING THE ILLNESS

The following questions are about your child's behavior during the illness.
Please select the box of the answer that best applies to your son/daughter's case.
7. During the last week, your child:

	Never	Sometimes	Often	Always
Has slept more than usual				
Has slept less than usual				
Has cried more than usual				
Has been more irritable				
Has had less desire to play				
Has been exhausted				
Has been less attentive				
Has needed more comfort				

8. In comparison to the previous week, your child's behavior has been: much worst, somewhat worse, the same, somewhat better, much better.

CONCERN ABOUT CHILD'S ILLNESS

The following questions are about what you felt as a father/mother about your child's disease.
Please select the box of the answer that best applies to your case.

9. During the last week, have you had the following feelings concerning your child's illness?

	No at all	A little bit	A lot	A great deal
Sadness to see my child being ill				
Impotence				
Mental exhaustion				
Physical exhaustion				
Guiltiness				
Fed up with the situation				

10. In comparison to the previous week, your emotions about your son/daughter's illness this week have been: much worst, somewhat worse, the same, somewhat better, much better.

YOUR DAILY ACTIVITIES DURING YOUR CHILD'S DISEASE

How much has your child's illness interfered in your daily activities?
Please select the box of the answer that best applies to your case.

11. During the last week and concerning your child's disease:

	0	1/2	1	2	3	4	5	6	7
How many nights did the illness disrupted your sleep?									
How many days did you have to dedicate exclusively to your child?									
How many days did you have to ask for help to someone else (parents, friends, neighbors…)?									
How many days could not he/she attend nursery school, or you could not leave him/her home with a babysitter?									

12. During the last week and concerning your child's disease:

	No at all	A little bit	A lot	A great deal
Have you lost sleep hours?				
Your child's illness limited your leisure time?				
Your child's illness limited the time for doing the groceries				
Your child illness limited the time for doing house chores				

13. Who has completed this questionnaire? Mother, Father or other.

A1.2: Satisfaction with treatment:

1: Overall, how happy were you with the treatment given in hospital?

1	2	3	4	5	6	7	8	9	10

Very unsatisfied Neutral Verry satisfied

2: If your child was given saline during treatment:

A: did your child react with crying or distress during administration of saline?

1	2	3	4	5	6	7	8	9	10

Strongly disagree Neutral Strongly Agree

B: Did you find that saline helped your child to clear the airways:

1	2	3	4	5	6	7	8	9	10

Strongly disagree Neutral Strongly Agree

3: After discharge, did you administrate saline to your child at home?

Yes	
No	

A2 Respiratory severity scoring with heart rate

Score	**Respiratory rate**	**Wheeze**	**Heart rate[a]**	SpOb2	**Accessory muscle use**
0	<30	None	<150	>95	None
1	30–45	End-expiratory only	151–160	94–95	Mild intercostal retractions
2	46–60	Entire expiration and inspiration with stethoscope	161–170	90–93	Moderate retractions
3	>60	Entire expiration and inspiration without stethoscope	>170	<90	Moderate retractions + head bobbing or tracheal tugging

[a]RSS-HR = respiratory rate + wheeze + heart rate + accessory muscle use
[b]RSS-SO = respiratory rate + wheeze + SpO_2 + accessory muscle use