BMJ Paediatrics Open

Normal saline for children with bronchiolitis: study protocol for a randomised controlled non-inferiority trial

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To cite: Schmidt MN, Daugberg R, Nygaard U, *et al*. Normal saline for children with bronchiolitis: study protocol for a randomised controlled non-inferiority trial. *BMJ Paediatrics Open* 2024;**8**:e002273. doi:10.1136/bmjpo-2023-002273

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjpo-2023-002273).

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Received 15 September 2023
Accepted 14 December 2023

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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 paediatric departments in Denmark use nebulised 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, multicentre, open-label, randomised, controlled non-inferiority trial and will be performed at six paediatric departments in eastern Denmark. We plan to include 300 children aged 0–12 months admitted to hospital with bronchiolitis. Participating children are randomised 1:1:1 to nebulised 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 hospitalisation, analysed 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 nebulisation, it may reduce the workload of nurses, and possible duration of hospitalisation because the treatment can be delivered by the parents at home.

Trial registration number NCT05902702.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bronchiolitis is among the primary reasons for hospitalisations of children during their first year of life.

⇒ Nebulised 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 nebulisation 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 nebulisation, 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 hospitalisations 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, apnoea 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 1 year old are admitted to the hospital due to bronchiolitis,[3] and accordingly, the disease exerts a substantial pressure on paediatric departments as well as the affected families. For the hospitals, children admitted with bronchiolitis stresses paediatric

acute care capacity in the winter months, and for society, the economic burden is considerable.

Although paediatricians 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 immunisation 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 paediatric departments, it has become common practice to use nebulised 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 non-invasive. However, some children find the treatment unpleasant and react by crying, which may potentially worsen respiratory distress. A secondary analysis of studies using nebulised NS as placebo when testing other treatments suggested that nebulised NS could improve symptoms of respiratory distress compared with an oral placebo.[11] In contrast, another study suggested that nebulised NS could cause airway obstruction.[12] A quality improvement study found that de-implementing the use of nebulised 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 hospitalisation or escalation of treatment.

NS is nebulised using pressurised 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 suggests 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 minimise 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 nebulised NS and nasal irrigation with NS in terms of duration of hospitalisation.

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 5 years after inclusion, to explore predictors of later development of respiratory disease among children admitted with bronchiolitis.

Table 1 Overview of the inclusion and exclusion criteria for saline treatment

Inclusion criteria	Exclusion criteria
Hospitalisation 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 nebulised 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, laboured breathing (tachypnoea, retractions, nasal flaring), grunting, cyanosis or apnoea, wheezing or crackles on auscultation, O_2 saturations below 92 %, difficulties feeding.
CPAP, continuous positive airway pressure; HFOT, high-flow oxygen therapy.

METHODS AND ANALYSIS

This study is an investigator-initiated, multicentre, open-label, three-arm randomised, 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 paediatric 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 minimise 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 nebulised 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.

Randomisation

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

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 randomised 1:1:1 to nebulised NS, nasal irrigation with NS or no saline therapy. Nebulised NS is administered by a nebulisation mask, supplied with pressurised air. Nasal irrigation with NS is administered first by the nurse, later by the parents. Both NS 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 hospitalisation. Duration of hospitalisation is defined as number of hours from admission until a doctor has evaluated that the child is ready for discharge.

Secondary outcomes are need for respiratory support with N-CPAP 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 randomised to; (4) highest pCO_2 measured; (5) Respiratory Severity Score with heart rate measured after treatment or every 3 hours if randomised to no saline treatment[15] (online supplemental file A2); (6) visible distress in the child during delivery of treatment (or every 3 hours if randomised to no saline treatment) using the Face, Legs, Activity, Cry, and Consolability (FLACC) scale[16 17]; (7) health-related quality of life (HR-QoL)[18] (online supplemental file A1.1) and (8) parents' satisfaction with the given treatment using a Likert scale (online supplemental file A1.2).

Participant timeline and follow-up

Recruitment of participants will start on 1 January 2024, and recruitment is expected to last for one and a half year through two seasons of bronchiolitis. After the 1-month follow-up, children will be followed as an observational cohort to investigate the long-term prognosis after admission with bronchiolitis. The children will be followed annually for 5 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 nebulised 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. Nebulised 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 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 (SAEs), defined as death, intubation or transfer to semi-ICU or ICU. 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 on admission, information will be collected about symptoms and treatment given at home, baseline health data

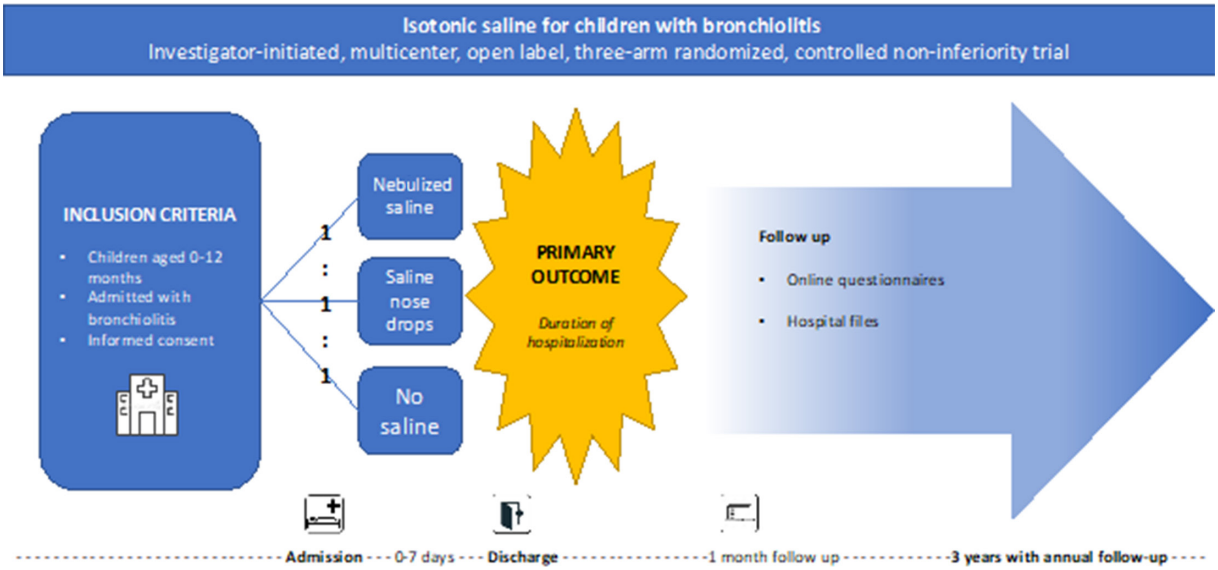

Figure 1 Study outline.

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 randomised to no saline, respiratory score and distress will be recorded every 3 hours.

Data collection will be standardised across sites using a standardised 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 1 month after discharge in REDCap, asking about the child's symptoms and the parent's experience and satisfaction with the hospitalisation and treatments offered, as well as HR-QoL.

Respiratory samples will be analysed 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 229E, 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 hospitalisation is estimated to be 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 nebulised 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

Anonymised data will be analysed in R statistics. Primary, secondary, exploratory and safety outcomes will be analysed according to the principles in an intention-to-treat analysis. As a secondary analysis, we will also analyse all outcomes as 'per-protocol', that is, only the randomised participants who have received the allocated treatment algorithm as defined in the protocol will be included.

The primary outcome (duration of hospitalisation) will be recorded as hours. The three groups (no saline vs nebulised NS, no saline vs nasal irrigation with NS, and nebulised NS vs nasal irrigation with NS) will be compared using linear regression and Cox regression analysis. The investigation is analysed 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 analysed 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.[21–23] For bronchiolitis, previously tested specific treatments include bronchodilators,[4] corticosteroids,[5] antibiotics[6] and nebulised 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 randomised, controlled trials, which will benefit patients and caregivers and enable prioritisation 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 nebulisation, it may reduce the workload of nurses, and possibly duration of hospitalisation, because the treatment can be delivered by the parents at home.

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Contributors The guarantors of the study are A-MMS and MHR 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 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 interests The authors declare no potential, perceived or real conflict of interest regarding the content of this manuscript.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The trial protocol has been approved by the Ethics Committee of Region Zealand with approval ID: EMN-2023-00012. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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