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Understanding the use and outcomes of high-flow nasal cannula among infants admitted to Canadian hospitals with bronchiolitis (CanFLO): a protocol for a multicentre, retrospective cohort study

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ABSTRACT

Introduction Bronchiolitis is the most common viral lower respiratory tract infection in children under 2 years of age. Respiratory support with high-flow nasal cannula (HFNC) is increasingly used in this patient population with limited understanding of the patients most likely to benefit and considerable practice variability of use. This study aims to understand the factors associated with failure of HFNC support among patients with bronchiolitis and to describe the current practice variations of HFNC use in patients with bronchiolitis in Canadian hospitals including fluid management and parameters to initiate, escalate and discontinue HFNC support.

Methods and analysis This is a multicentre retrospective cohort study including hospitalised patients aged 0–24 months with bronchiolitis requiring support with HFNC between January 2017 and December 2021. Clinical data will be collected from patient medical records from Canadian hospitals (n=12), including academic and community centres. HFNC failure will be defined as the need for escalation to non-invasive or invasive mechanical ventilation. Factors associated with HFNC failure will be analysed using logistic regression. Descriptive statistics will be used to describe practice variations of HFNC utilisation and management.

Ethics and dissemination Approval from the Research Ethics Boards (REBs) has been obtained for each participating study site prior to onset of data collection including Clinical Trials Ontario for all Ontario hospital sites and REBs from British Columbia Children's Hospital, Stollery Children's Hospital, Montreal Children's Hospital and CHU Sainte-Justine. Study results will be disseminated through presentation at national/international conferences and publication in high-impact, peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study describing risk factors for high-flow nasal cannula (HFNC) failure among patients with bronchiolitis will provide a better understanding of both the current practice variation of HFNC use and the risk factors for requiring escalation of respiratory support and will be beneficial for future development of protocols for HFNC management of hospitalised patients with bronchiolitis.
⇒ The inclusion of both tertiary and community hospital sites increases generalisability of study results.
⇒ As a retrospective design, data collection will be limited to information that is documented and available in patients' records.

INTRODUCTION

Bronchiolitis is a viral lower respiratory tract infection that is characterised by small airway inflammation and obstruction.[1] It is the most common lower respiratory tract infection in children under 2 years of age and is a cause of significant morbidity and burden on the healthcare system.[2] Bronchiolitis is the most common reason for hospital admission in children less than 12 months of age,[3] and similarly is one of the most common reasons for non-elective paediatric intensive care unit (PICU) admission.[4] Several patient factors including history of prematurity, chronic lung disease, neuromuscular disease, immunodeficiency and age less than 6 months have been associated with more severe disease.[2 4] However, despite its prevalence, there is significant variability in the management of bronchiolitis, with current evidence only suggesting supportive treatment including hydration and supplemental oxygen.[5]

Traditionally, escalation of respiratory support in bronchiolitis follows the trajectory of low-flow oxygen (LFO), to continuous positive airway pressure (CPAP), to invasive mechanical ventilation.[3] The latter two contribute to significant PICU burden. Increasingly, respiratory support with high-flow nasal cannula (HFNC) has been used among patients with bronchiolitis both as a rescue therapy and as initial respiratory support despite limited evidence of its efficacy and safety in this patient population.[6] Among patients with bronchiolitis, HFNC is hypothesised to be effective with the theory that higher flow rates of warm, humidified gas are able to (1) provide a consistent fraction of inspired oxygen (FiO_2); (2) reduce upper airway resistance; (3) wash out nasopharyngeal dead space; and (4) provide some positive end-expiratory pressure, although not titratable as with CPAP.[7] From a health systems perspective, HFNC is attractive as it provides the potential to be used outside of the PICU setting.[2 8]

Several studies have described the use of HFNC for the support of moderate-to-severe respiratory distress in bronchiolitis in comparison with non-invasive ventilation (NIV), including CPAP and LFO. Metge *et al* demonstrated that support with HFNC is comparable with that of CPAP regarding length of stay (LOS) in PICU as well as in resolution of respiratory distress, defined by improving trends in vital signs, venous partial pressure of carbon dioxide (pCO_2) and oxygen requirements.[9] Similarly, Pedersen and Vahlkvist describe that the use of both HFNC and CPAP results in similar treatment duration and LOS in PICU, although patients treated with CPAP were found to have a faster initial improvement in respiratory rate and FiO_2 needs.[10] Vahlkvist *et al* demonstrated similar improvement in respiratory rate, pCO_2, FiO_2 and the modified Woods Clinical Asthma Score when comparing CPAP with HFNC but found improved pain scores in the HFNC group suggesting better tolerability and comfort with HFNC.[11] In two recent systematic reviews, it was concluded that in comparison with both CPAP and LFO, there is no difference in hospital LOS or length of oxygen requirement when HFNC is used for management of respiratory distress in bronchiolitis.[6 12] Rates of treatment failure are significantly lower in patients supported with HFNC compared with traditional LFO.[8 13 14] Treatment failure for HFNC is often defined as progression of respiratory support, for example, NIV or invasive ventilation.[15–21] For this study, we have adopted a similar definition. There remains conflicting evidence as to whether HFNC is comparable with CPAP in regard to rates of treatment failure with Milesi *et al* and Habra *et al* describing higher rates of treatment failure among HFNC compared with CPAP, while Vahlkvist *et al* demonstrated no significant difference in rates of treatment failure between the two forms of respiratory support.[11 22 23] Furthermore, since the introduction of HFNC, there has been no change to overall intubation rates in patients with bronchiolitis; however, average LOS in PICU has decreased.[24] The utilisation of PICU resources, however, has increased for patients with bronchiolitis between 2004 and 2018, theorised in part to be due to increased utilisation of HFNC without clear guidelines for its utilisation.[25] There is an ongoing need to identify the patient population who will optimally benefit from HFNC support in comparison with other modalities of respiratory support.

Identifying patient factors that are associated with HFNC treatment failure will allow for identification of the patient population who are most likely to require escalation to invasive respiratory support. Within the literature, it has been found that higher venous pCO_2 and lower venous pH predict HFNC treatment failure within the general paediatric population.[15 16 18 26] The role of the medical history in contributing to predicting treatment failure is less described. Betters *et al* suggest that HFNC failure is more likely in children with a history of cardiac disease or previous intubation, while Kelly *et al* report no correlation between medical history and treatment outcome.[16 27] High initial FiO_2 requirements,[16 28] respiratory rate greater than the 90th percentile for age[16] and low oxygen saturation (SpO_2)-to-FiO_2 ratio[17 26] have also been described as predictors of failure of HFNC therapy.

Specific to patients with bronchiolitis, younger age has been repeatedly associated with HFNC treatment failure.[20 21 29 30] Clinical evidence of dehydration with poor feeding[29] as well as need for nasogastric (NG) hydration at any time during HFNC treatment course have also been associated with HFNC failure.[19] Clinical parameters associated with HFNC failure in bronchiolitis include tachycardia[20 31] and evidence of increased work of breathing in the form of nasal flaring, grunting and retractions.[29] Clinical scoring tools incorporating vital signs and physical examination findings have also shown to be of value in predicting HFNC failure with a Modified Tal Score greater than 5 at 4 hours of HFNC therapy associated with treatment failure,[21] and Suessman *et al* reporting higher Clinical Respiratory Tool scores predictive of failure.[20] Laboratory markers consistent with HFNC failure include elevated pCO_2[15 18] and pH less than 7.3.[31] It has also generally been found that patients with bronchiolitis who fail HFNC therapy are more likely to do so early in their treatment course with Suessman *et al* describing that greater than 50% of patients requiring intubation after failure of HFNC did so within 6 hours of HFNC initiation.[20] In a study by D'Alessandro *et al*, the median time to HFNC failure was 10 hours,[21] which is similar to results found by Abboud *et al* and Nascimento *et al* who report average times to HFNC failure of 14 and 12.8 hours, respectively.[15 19] This further supports the need to identify the optimal patient population for HFNC support and to better understand the characteristics of children who are likely to require additional clinical support such as escalation to NIV and transfer to centres with intensive care support. The overarching objective of this study is to understand the factors associated with HFNC failure among hospitalised patients with bronchiolitis in Canada.

METHODS

Study design

This study will be a multisite retrospective cohort study investigating hospitalised patients with bronchiolitis requiring support with HFNC between January 2017 and December 2021. The study will be conducted by the Canadian Pediatric Inpatient Research Network and include both tertiary academic children's hospitals and community hospitals (n=12). The coordinating study site is McMaster Children's Hospital (Hamilton, Ontario). Additional academic children's hospital sites include: British Columbia Children's Hospital (Vancouver, British Columbia), Stollery Children's Hospital (Edmonton, Alberta), Children's Hospital at London Health Sciences Centre (London, Ontario), The Hospital for Sick Children (Toronto, Ontario), Kingston Health Sciences Centre (Kingston, Ontario), Children's Hospital of Eastern Ontario (Ottawa, Ontario), Montreal Children's Hospital (Montreal, Quebec) and CHU Sainte-Justine (Montreal, Quebec). Community/regional hospital sites include: Windsor Regional Hospital (Windsor, Ontario), Grand River Hospital (Kitchener-Waterloo, Ontario) and Lakeridge Health (Oshawa, Ontario). Additional hospital sites may be added based on feasibility and resources. Study recruitment will be closed prior to onset of data analysis. The study will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies.[32]

Study population

This study will include patients aged 0–24 months admitted to and discharged from hospital between 1 January 2017 and 31 December 2021, inclusive, with a clinical diagnosis of bronchiolitis, based on assigned diagnosis at the time of hospital admission or discharge by the most responsible physician, who were supported with HFNC. For the purpose of this study, clinical diagnosis of bronchiolitis will be defined based on International Classification of Diseases, 10th Revision, Canada diagnostic codes for bronchiolitis. Included codes will be: J21.0 (acute bronchiolitis due to respiratory syncytial virus), J21.1 (acute bronchiolitis due to human metapneumovirus), J21.8 (acute bronchiolitis due to other specified organism) and J21.9 (acute bronchiolitis, unspecified). Records will be excluded if (1) they received NIV or invasive ventilation prior to the initiation of HFNC, (2) if they have a tracheostomy, or (3) if they receive chronic home oxygen or respiratory support, including CPAP or any other form of NIV. For patients with multiple admissions meeting inclusion criteria as defined, only their first admission will be captured in data analysis to avoid duplication of data.

Objectives

The *primary objective* of this study will be to understand the factors associated with HFNC failure among hospitalised patients with bronchiolitis including patient demographics, clinical features and laboratory markers. The *secondary objectives* will describe current practice variations in the use of HFNC across multiple Canadian hospitals, including:

a. Differences in methods of nutrition and fluid management, including use of oral and NG nutrition and intravenous fluids.
b. Clinical parameters guiding HFNC use and discontinuation including:
   - Severity of respiratory distress at the time of HFNC initiation and, if applicable, time of escalation to NIV or mechanical ventilation.
   - Time from hospital presentation to initiation of HFNC.
   - Variability in device settings including flow rates and FiO_2 used at time of initiation and weaning.
   - Location within hospital setting of use.
   - Respiratory support used at the time of escalation or de-escalation from HFNC.
   - Hospital characteristics.

Data collection

Data will be collected from electronic and paper patient medical records, the specifics of which will vary between participating sites. A primary site investigator at each participating hospital will identify eligible patients for inclusion based on the criteria outlined above. The site investigators will identify and train a research assistant who will be responsible for data collection using a standardised case report form. Included patient charts will be assigned a unique study identification number and de-identified data will be entered directly into a secure Research Electronic Data Capture (REDCap) online database that will be managed at McMaster Children's Hospital, Hamilton Health Sciences, and supported by the Population Health Research Institute in Hamilton, Ontario.

Patient demographic data will include age at time of admission (months), gestational age, sex, admission weight (kg) and any significant medical history. Significant medical history will be categorised as congenital cardiac disease, chronic lung disease, neuromuscular disease, immunodeficiency, home enteral tube feeding, history of allergies or eczema, history of wheeze or use of bronchodilators, and failure to thrive. Hospital demographic data will include whether the hospital is an academic tertiary, academic community or community hospital. Rural versus urban location of the hospital, the average number of paediatric medicine admissions to the hospital per year, as well as presence of an in-house physician or delegate and dedicated paediatric respiratory therapist will be recorded. For each participating hospital site, the availability of and location(s) of use of HFNC throughout the study duration will be collected as well as manufacturer details of HFNC devices used where available.

Clinical characteristics will include documenting fluid and nutrition management during admission. The use of oral (PO), intravenous or NG fluids at any time while

on HFNC will be recorded. The time to first feeding and feeding type while on HFNC, including PO, NG or other forms of enteral feeding, will be captured. The pH and pCO_2 (specified from venous, capillary or arterial sample) from the first recorded blood gas of the hospital admission will be collected, as well as date and time of sample. Results of viral testing such as nasopharyngeal swab or wash will also be collected and categorised as respiratory syncytial virus, COVID-19 or other (eg, rhinovirus, enterovirus, adenovirus, influenza, parainfluenza and metapneumovirus). The use of the following at any time during HFNC use will also be captured: nebulised epinephrine, salbutamol, corticosteroids, antibiotics and hypertonic saline.

Time of hospital admission and discharge, as well as time of emergency department (ED) triage, will be recorded. ED triage score, Canadian Triage and Acuity Scale will also be documented. Time (hours) between presentation to hospital and initiation of HFNC will be collected. Clinical setting where HFNC is used, both at time of initiation and discontinuation, will be recorded including PICU, general paediatric ward, paediatric ED community hospital or other. Any time spent in a PICU will also be documented. Documented HFNC parameters will include initial flow rate (L/kg/min) and FiO_2 (%), maximum flow rate (L/kg/min), time spent at maximal flow rate, FiO_2 (%) when maximal flow rate first achieved, FiO_2 (%) just prior to weaning maximal flow rate or escalation of support, flow rate (L/kg/min) and FiO_2 (%) immediately prior to HFNC discontinuation (for responders) and immediately prior to escalation of respiratory support (for failures) and duration of HFNC therapy (hours).

Clinical parameters including respiratory rate, heart rate, SpO_2 (%), FiO_2 (%), presence of wheeze or crackles, and presence of accessory muscle will be documented at the time of HFNC initiation, 4 hours post-initiation, and, if applicable, at the time of escalation from HFNC to either NIV or mechanical ventilation (for HFNC failures) or at the time of initial wean (for HFNC responders). A Modified Tal Score will be calculated for the aforementioned time points based on available documentation, which includes respiratory rate, SpO_2, accessory muscle use, and the presence of wheeze or crackles on auscultation.[33] Type of respiratory support required immediately after HFNC discontinuation will be collected and categorised as: (1) room air, (2) LFO, (3) NIV including CPAP, bilevel positive airway pressure and nasal intermittent positive pressure ventilation, or (4) intubation and mechanical ventilation. For patients transferred to a tertiary hospital while on HFNC, records from the tertiary hospital will be reviewed to determine type of respiratory support required post-transfer. If the management post-hospital transfer is unavailable to study investigators, the respiratory support post-HFNC will be classified as (5) unknown.

Outcomes

Primary objective

Patients will be classified within a binary outcome of HFNC responder and HFNC failure. HFNC responder will be defined as a patient successfully coming off HFNC and transitioned to LFO or room air. HFNC failure will be defined as a patient requiring escalation of respiratory support to NIV and/or invasive mechanical ventilation.

Secondary objectives

Fluid and nutrition management will include description of the use of intravenous, NG or PO fluids at any time during HFNC use as well as time from HFNC initiation to first enteral feeding. Clinical parameters guiding HFNC use will capture location of HFNC initiation and discontinuation including any time spent in a PICU setting, time from hospital presentation to HFNC initiation, total time spent on HFNC support, severity of respiratory distress at the time of HFNC initiation/escalation/weaning as defined by patient vital signs and Modified Tal Score, device settings including flow rate (L/kg/min) and FiO_2 (%) at HFNC initiation/maximum support/time of escalation/time of weaning, and type of respiratory support implemented after HFNC use. Description of hospital characteristics will include whether the hospital is located in a rural or urban environment, if the hospital is a community or tertiary centre, the average number of paediatric medicine admissions per year, distance to tertiary-level children's hospital, presence of in-house physician overnight and presence of a dedicated paediatric respiratory therapist.

Statistical plan

Baseline characteristics will be reported using descriptive statistics, continuous variables will be reported as means and SDs, and categorical variables will be reported using percentages. Normality of the variables will be examined using tests of skewness, and variables will be reported as medians and quartiles or be transformed. Primary objective: univariate logistic regression will be used to explore clinical and biochemical factors associated with the outcome, failure of HFNC. A priori variables included will be: age, gestational age, sex, history of significant medical condition, feeding support and fluid management, medication use, pH, pCO_2, viral testing, Modified Tal Score and HFNC variables (total duration, flow rates (initial and maximum) and FiO_2 (initial and maximum)). After testing for multicollinearity, uncorrelated factors will be included in the multivariable logistic regression analysis. In these models, covariates will be entered as a block. Goodness of fit will be assessed by examining the residuals for model assumptions and using the Hosmer and Lemeshow goodness-of-fit test. ORs, 95% CIs and p values will be reported. Secondary objective: descriptive statistics will be used to report management of hydration and clinical parameters guiding HFNC use, as well as differences in timing of HFNC weaning (eg, day 1 vs 3 as surrogate of severity), age (<12 vs >12 months) and feeding status.

Sample size considerations

For the study including 12 sites, we estimate approximately 2000 charts will be included. This will allow us to adjust for >15 variables in multivariable models, assuming small effect size and a power of 80%, with a significance level of 0.05. These computations were done using WINPepi.[34] We estimate that 30% of patients will require respiratory support, additional to HFNC (ie, fail HFNC).

Data storage and management

Local site investigators will be responsible for ensuring the secure collection and storage of patient data. All patient charts will be assigned a unique study identification number. The key linking the study identification number to patient medical record number will be kept separate from extracted data and only accessible to the local site investigator at each participating hospital. Once assigned a study identification number, de-identified patient data will be input directly into a secure, password-protected electronic database (REDCap). Any physical copies of patient records will be stored in a locked office and accessible only to members of the local research team.

Patient and public involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION

Ethical considerations

Research ethics approval has been obtained for each participating study site, including Clinical Trials Ontario (CTO 3965) for all Ontario hospital sites and local Research Ethics Board approval for non-Ontario sites including British Columbia Children's Hospital (H22-01736), Stollery Children's Hospital (Pro00124103), Montreal Children's Hospital (MP-37-2023-9056) and CHU Sainte-Justine (MEO037-2023-4958, MP-37-2023-9056). Given the retrospective nature of this study, it is impractical to obtain consent from the participants. Direct harm is minimal with the main risk here being a breach of privacy regarding collected data. This harm will be minimised using the strategies outlined under data storage and management. The information being collected will be used in a manner that will ensure its confidentiality. The research purposes cannot be achieved without the information being extracted from patient charts. It is the belief of the investigative team that the public interest in conducting the research exceeds the risk of breach of privacy of the individuals.

Dissemination and data sharing

All data will be shared among the study team. Participating sites may request access to study data for use in subsequent studies. The principal investigator will be responsible for data analysis and subsequent correspondence. Study results will be disseminated widely by both presentation at national/international conferences and publication in high-impact peer-reviewed journals.

DISCUSSION

To our knowledge, this is the largest study describing risk factors for HFNC failure among patients with bronchiolitis. In addition, this is the first multicentre study describing the current practice variability of HFNC use in hospitalised patients with bronchiolitis in Canada. Currently, there are no accepted guidelines for the optimal timing of implementation, utilisation or need for escalation of HFNC in patients with bronchiolitis. An understanding of both the current practice variation of HFNC use and the risk factors for requiring escalation of respiratory support in this population will therefore be beneficial for future development of protocols for HFNC management of hospitalised patients with bronchiolitis. In addition, the inclusion of both community and academic hospitals in the study design increases generalisability of results to all hospitals in which care of this patient population is provided.[28 35 36]

Given the retrospective design of this study, there will be some limitations in collected data based on available documentation in the patient medical records. To minimise large gaps in data collection, prior to formal study initiation, the case report form will be piloted centrally and reviewed by participating centres to ensure that intended data to be collected will be accessible. Second, screening patients for study inclusion using International Classification of Diseases codes for bronchiolitis may miss some patients who should have been included either due to transcription error or in clinical scenarios where the patient may have developed subsequent complications that then were listed as the primary discharge diagnosis. Due to the projected large sample size of this study, we feel that the study population will still be adequately representative. The specific outcomes of patients who are transferred out of a study centre while still on HFNC may be unknown if the receiving hospital is not a participating study site. In this clinical scenario, we will code the outcome as transferred from the community site, and if able record the outcome at the tertiary hospital if they are a study site. Lastly, as the study includes the time period of the COVID-19 pandemic, there may be impacts on the overall patient population and practice patterns.

Despite increasing literature on the topic, there are currently no accepted guidelines for the use of HFNC in patients with bronchiolitis and the optimal role and benefits of HFNC support in this population remain unclear. Understanding the factors that can predict which population of patients with bronchiolitis are most likely to benefit from HFNC therapy versus the population most likely to fail and require more invasive forms of respiratory support that can only be provided in an intensive care setting is key to being able to define the optimal role of

HFNC therapy in hospitalised patients with bronchiolitis. Furthermore, understanding the current practice variations of HFNC use in this population among different Canadian centres will identify knowledge gaps and opportunities for streamlining and unifying current practice models. Given the heterogeneous locations where this patient population is cared for, inclusion of both tertiary and community hospitals in this study is imperative to better understand the ideal role of HFNC in patients with bronchiolitis.

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Contributors MD'A and GW conceived the study and drafted the manuscript. MD'A, LM and GW designed the study and the statistical analysis plan. MD'A, CF, FA, NB, JSB, OD, JLF, LG, PJG, RG, PL, JMc, JMe, MS, CS, AS, NS, LM and GW participated in the development of the protocol, data acquisition methods and manuscript revisions, and have read and approved the final version of the manuscript.

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