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"Rational use of high-flow therapy in infants with bronchiolitis. What do the latest trials tell us?" A PREDICT perspective.

Main Text:

"One of the general methods to be adopted in the treatment of acute bronchiolitis is that these children should be nursed in warm moist air, with an adequate oxygen supply." [1]

- D Hubble and GR Osborn. BMJ, 1941

Bronchiolitis, caused by viral lower respiratory tract infections, is the most common reason for infants aged less than one year of age to be admitted to hospital. Various therapies have been studied over the years, with little demonstrable benefit. A multidisciplinary committee systematically reviewed the bronchiolitis literature in 2015 and using the robust Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the National Health and Medical Research Council (NHMRC) methodologies developed the Australasian Bronchiolitis Guideline[2] for the management of infants presenting to and admitted into Australasian hospitals with bronchiolitis. This guideline recommended against the use of beta-agonists, corticosteroids, adrenaline, antibiotics, antivirals and hypertonic saline in infants with bronchiolitis, with the pillars of recommended therapies being support of hydration and respiration.[2]

Over the last decade high-flow nasal cannula (HFNC) therapy has been increasingly used for respiratory support in infants admitted to hospital with bronchiolitis. HFNC use was initially confined to the intensive care unit (ICU) setting but has now broadened to include emergency departments (EDs) and general paediatric wards. At

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the time of writing the Australasian Bronchiolitis Guideline,[2] studies on the use of HFNC in bronchiolitis were limited to low quality and observational evidence, mainly confined to the ICU setting, with very limited studies on the utility of HFNC use in EDs and inpatient wards. As such, Guideline recommendations regarding the use of HFNC for bronchiolitis were: (1) in non-hypoxic infants, its use should be confined to randomised controlled trials (RCTs), and (2) in hypoxic infants (oxygen saturations less than 92%) a low level recommendation (NHMRC: C, GRADE: Conditional) to consider HFNC. Subsequent to the 2015 systematic literature search for the Australasian Bronchiolitis Guidelines, a number of RCTs have published their results, in particular three major studies.[3-5] This paper updates the systematic literature review regarding HFNC use in bronchiolitis used for the Australian Bronchiolitis Guideline, summarizes and critiques the new RCTs, and provides evidence-based recommendations for the use of HFNC to manage bronchiolitis in ED and ward settings.

What is high-flow nasal cannula therapy?

HFNC therapy is a form of respiratory support in which flow rates of humidified, heated gas are delivered into the nasal passages at higher rates of flow than that which is traditionally delivered via standard sub nasal oxygen therapy. HFNC therapy can be delivered at a rate of up to 2-3 L/kg/min, with a maximum of 60 L/min,[6] whilst traditional sub nasal oxygen therapy is usually delivered up to a maximum of 2-3 L/min. Mechanisms of action of HFNC therapy are uncertain, although thought to involve some aspects of the following: washout of nasopharyngeal dead space, reduced upper airway resistance, and provision of a degree of positive pressure.[7] As bronchiolitis is a disease of the small and medium airways, HFNC has become an attractive modality to overcome hypoxia and potentially increased respiratory work associated with bronchiolitis.

Literature search

Using the same search strategy (Appendix 1and 2) and methodology[8] as the current Australasian Bronchiolitis Guideline[2] the following databases were searched: Ovid Medline, Ovid Embase, PubMed, Cinahl (EBSCO), Cochrane Library, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) for systematic reviews and RCTs from 1 Jan 2000 to 27 June 2018. Once studies were identified, one author screened the title and abstracts of the articles identified for systematic reviews and RCTs relevant to HFNC use in infants with bronchiolitis. Copies of the identified articles were retrieved, then reviewed by three authors for eligibility and data extracted. The search strategy identified 34 new articles since 2015, three RCTs and no systematic reviews, relevant to HFNC use in infants with bronchiolitis.

Evidence for high-flow nasal cannula therapy in bronchiolitis

The evidence base for the recommendations regarding HFNC in the Australasian Bronchiolitis Guideline was based upon a 2014 Cochrane systematic review,[7] one evidence based guideline,[9] one RCT,[10] two prospective studies,[11, 12] four non-systematic reviews,[13-16] and one retrospective cohort review.[17] The single RCT identified was a small trial of HFNC vs. hypertonic saline in 75 infants with bronchiolitis from two Spanish hospitals. In our subsequent systematic literature search three further RCTs have been identified involving 1,816 participants. Thus, there have now been four RCTs, in 1,891 participants, of HFNC in infants with bronchiolitis: three of these studies involved infants treated in EDs and inpatient paediatric wards in Spain, Australia and New Zealand,[3-5] and one study involved infants treated in paediatric ICUs in France[4] (***Table 1***).

The three studies conducted outside of ICU differed in important areas and of concern, significant variation in the amount of supplemental oxygen entrained with the HFNC as highlighted in Table 1. Franklin *et al.*[5] enrolled patients with oxygen saturations < 92-94% (depending on individual institution cut offs for hypoxia) and used flow rates of 2 L/kg/min. Kepreotes *et al.*[3] excluded infants with saturations <

90%, mainly enrolled infants with oxygen saturations > 94% and used flow rates of 1 L/kg/min. Campaña *et al.*[10] used a non-validated clinical score (which includes oxygen saturations as one component) to define eligibility, but do not report the final oxygen saturation of the included participants, and used a calculation of tidal volume and respiratory rate to determine the flow rate of HFNC delivered, although the delivered flow at 6-8 L/min is likely approximately 1 L/kg/min. The primary outcomes and the definition of treatment failure itself also differed between the three studies. Franklin *et al.*[5] used treatment failure as the primary outcome, defined as escalation of care and e 3 out of 4 pre-specified physiological endpoints (persistent or increased tachycardia; persistent or increased tachypnea; hypoxemia (FiO_2 of e 0.4 if on HFNC, or >2 L/min if on nasal cannula, to maintain SpO_2 e 92-94%); medical review triggered by a hospital early-warning tool). Kepreotes *et al.* used time on oxygen therapy as the primary outcome, and defined treatment failure as escalation of care and the presence of one of four slightly different physiological endpoints to those used by Franklin *et al* (critically abnormal observations that fell within the red zone on an age-appropriate standard paediatric observation chats for heart rate, respiratory rate, SpO2 <90%, or severe respiratory distress score while on maximum therapy). Meanwhile, Campaña *et al.* used a non-validated, not routinely used, clinical score as their primary end-point and did not define or report treatment failure. Additional concerns regarding the quality of the RCT evidence include the small sample size, lack of a comparison arm of standard clinical care, and multiple comparisons in the Campaña *et al.* trial; single centre design in the Kepreotes *et al*. trial; and the reporting of the main primary outcome in the Franklin *et al.* study differing from the protocol (however, both outcomes clearly reported), with a differing effect size between sites with and without an ICU (**Table 1**).

The Milesi *et al.*[4] trial enrolled infants with bronchiolitis requiring ICU admission comparing HFNC therapy and nasal continuous positive airway pressure (nCPAP) therapy. The authors used a modified Wood's clinical asthma score (mWCAS) (which includes oxygen saturations as one component and is deemed appropriate to

use in infants with bronchiolitis)[18] to define infants for enrolment, using HFNC at 2 L/kg/min. Their primary outcome was treatment failure based on deterioration in the asthma clinical score, comfort score, respiration rate, or presence of two apnoeas in an hour (**Table 1**).

All RCTs evaluating HFNC are non-blinded studies. While this design feature is not avoidable, due to the nature of the experimental therapies being compared, it introduces a potential for bias.

Results of the RCTs are presented in **Table 2**. Notably, both Franklin *et al.* and Kepreotes *et al.* (n=1,674) reported fewer treatment failures (although using different definitions, **Table 1**) with HFNC than with standard care. However, these RCTs found no difference in ICU admission rates, intubation rates, duration of oxygen therapy, or hospital length of stay between those initially commenced on standard sub nasal oxygen therapy and those commenced on HFNC. In the ICU setting Milesi *et al.* (n=142) found that nCPAP was superior to HFNC with less treatment failures.[4] All three RCTs allowed the use of rescue HFNC. In the 200 infants who failed standard sub nasal oxygen in the two non-ICU RCTs, HFNC effectively rescued (no ICU admission) 61%. Similarly, in the ICU RCT, for the 22 infants who failed nCPAP, HFNC rescued (no need for further respiratory support) 82% (**Table 3**).

No adverse events were reported by Milesi *et al.*[4] and Campaña *et al.*[10] Kepreotes *et al*[3]. reported four adverse events, two in each arm of the study, all deemed not serious; one HFNC patient inhaled condensation from the HFNC circuit, one HFNC patient and two standard sub nasal oxygen patients received brief periods of room air due to lack of connection to oxygen or oxygen tubing discontinuation.[3] Franklin *et al.* reported two cases of pneumothorax, with one occurring in each arm of the study.[5] These are the only pneumothoraces reported in each of the combined HFNC and comparison arms for the three RCTs that reported this outcome (n=1,816). Thus HFNC appears safe to use in patients with bronchiolitis.

Kepreotes *et al.*[3] undertook a health economic analysis comparing initial standard sub nasal oxygen without rescue HFNC, compared to initial HFNC and initial standard sub nasal oxygen with rescue HFNC in ED and the ward environment. The most cost-effective treatment strategy in their analysis was initial standard sub nasal oxygen with rescue HFNC, closely followed by initial HFNC therapy. A formal health economic analyses of the other three studies has not been published to date. However, major drivers of cost in bronchiolitis management include hospital length of stay and ICU admission (neither of which have been shown to be improved with initial HFNC), and consumable costs, which are higher with HFNC than standard oxygen therapy. Any formal health economic analysis would be very unlikely to show benefit of a strategy employing initial HFNC compared to a strategy of initial standard sub nasal oxygen with rescue HFNC if needed.

Updated evidence tables using GRADE and NHMRC methodologies

The addition of the new RCT evidence has allowed for more definitive recommendations to be formulated using the GRADE and NHMRC approaches (**Table 4; Appendix 3 and 4**).

When should I use high-flow nasal cannula therapy for a child with bronchiolitis?

The usual clinical course for infants with bronchiolitis is worsening symptoms over 3 to 5 days followed by improvement over the next 7 to 10 days. Within this predictable clinical course there is further variation in clinical appearance with at times minute-by-minute clinical variation.[9] This variation can be attributed to discomfort, hunger, hypoxia or mucus plugging, and makes prediction of clinical projection problematic. Thus, there will be times when clinical observations breach "acceptable" physiologic parameters and lead to medical review, for the physiologic parameters to self-settle, while other breaches will reflect true clinical deterioration.

The definition of "treatment failure" in the two largest RCTs conducted in the ED and paediatric ward setting was based on escalation of care in response to clinical parameters; however, there were differences in this definition between studies, and differences in interpretation between sites with and without an ICU in Franklin *et al*.,[5] reflecting a lack of objective consensus between clinicians on this topic. In these two RCTs all patients in the standard sub nasal oxygen therapy arm who failed therapy escalated initially to HFNC (with the exception of one infant in Kepreotes *et al.*[3] who became distressed on standard sub nasal oxygen but subsequently stabilised in room air while being assessed. Both these studies utilised paediatric early warning scores as part of their definitions of failure.

Early warning scores are a numeric score generated from predetermined physiological criteria and observations, and are utilised to alert staff to clinically deteriorating patients and widely used in some countries.[19] Without a better alternative, and until further evidence is available regarding the utility of paediatric early warning scores, utilising these widely used tools, and their components, appears appropriate to define failure. Using paediatric early warning tools to define failure, the two large non-ICU RCTs demonstrated a good "success" rate of standard sub nasal oxygen therapy of 67%[3] to 77%,[5] and a relatively high ability of high-flow to "rescue" those "failing" standard oxygen therapy (61%).[3 5]

When infants with bronchiolitis are initiated on standard sub nasal oxygen therapy response to therapy is not going to be immediate. However, observational evidence supports that by 4 hours clinicians should see reduction in heart rate, respiratory rate and paediatric early warnings scores.[20] Therefore clinicians should wait this amount of time before deciding if a patient initiated on standard sub nasal oxygen therapy can be deemed a "failure."

Clinical Bottom line

Given the ease with which care can be escalated to HFNC if needed, and that two thirds of infants in the largest studies did not require escalation past standard sub nasal oxygen therapy, initial treatment for infants with bronchiolitis and hypoxaemia should be sub nasal oxygen therapy up to 2 L/min to maintain oxygen saturations, with HFNC reserved for cases of deterioration after the use of standard subnasal oxygen therapy (**Figure 1**). The evidence from RCTs and health economic analysis undertaken to date do not support primary treatment with HFNC therapy in the emergency and ward setting. If HFNC is ineffective in the ward setting, then transfer to a higher level of care, and consideration of nCPAP appear to be reasonable next steps. The use of HFNC for work of breathing in the absence of hypoxaemia, and severe disease, is not currently supported by the evidence, and should only be considered in the context of an appropriate research trial.

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