Editorial

High flow nasal cannulae for acute viral bronchiolitis in young infants: evidence-based medicine is underway to define target populations and optimal flows

Gilles Cambonie[1], Marti Pons-Odena[2], Julien Baleine[1], Christophe Milési[1]

[1]Pediatric Intensive Care Unit, Arnaud de Villeneuve Hospital, Montpellier University Hospital Centre, Montpellier, France; [2]Pediatric Intensive Care Unit, Sant Joan de Deu University Hospital Centre, University of Barcelona, Esplugues de Llobregat, Barcelona, Spain

Correspondence to: Gilles Cambonie, MD, PhD. Department of Neonatology, Neonatal and Pediatric Intensive Care, Arnaud de Villeneuve University Hospital and Montpellier School of Medicine, 371 Avenue du Doyen G Giraud, 34295 Montpellier Cedex 5, France. Email: g-cambonie@chu-montpellier.fr.

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Over the last decade, high flow nasal cannulae (HFNC) have increasingly been used for oxygen delivery in neonatology departments, gradually replacing nasal continuous positive airway pressure (nCPAP). Their use in pediatrics departments is more recent and generally is focused on infants with acute viral bronchiolitis (AVB) (1). New treatments often generate pendulum swings, from great resistance to great enthusiasm and back, until the appropriate target population is found. At the outset, cohort studies suggested a lower intubation rate in patients receiving HFNC treatment (2,3). A later study in an emergency department found that, among children with respiratory distress, those diagnosed with AVB showed better responses to treatment with HFNC (4). The increasing use of preemptive HFNC for the initial management of AVB has been associated with low (<10%) intubation rates in key observational studies (2-6), progressively positioning this device as an alternative to nCPAP, the gold-standard respiratory support for moderate to severe AVB.

A recent multicenter randomized controlled trial directly compared HFNC and nCPAP for primary respiratory support in young infants hospitalized in a pediatric intensive care unit (PICU) (7). The primary endpoint was the percentage of failure within 24 h of randomization, defined as the occurrence of one or more of the following: increase in respiratory distress score or respiratory rate, increase in discomfort, and severe apnea episodes. The study included 142 infants, equally distributed into groups. A –19% difference in the risk of failure (95% CI: –35% to –3%) was observed, in favor of nCPAP. As the prespecified one-sided non-inferiority margin of –15% was included in the confidence limit, the data did not allow the conclusion of non-inferiority (P=0.707). Indeed, superiority analysis suggested the relative probability of success to be 1.63 (95% CI: 1.02–2.63) higher with nCPAP. In addition, the reasons for failure differed between groups, mainly worsening respiratory distress with HFNC and discomfort with nCPAP.

On a practical level, HFNC efficacy in cases of respiratory failure depends on matching the patient's inspiratory demand with the delivered flow rate (8). In normally breathing neonates and infants, data on peak tidal inspiratory flow are very scarce, possibly ranging between 0.83 and 2.5 L/kg/min (9,10). Inspiratory demand increases during respiratory distress, but precise data are sorely lacking to adjust flow rate settings. This is thus a research direction to pursue to reduce the risk of failure when using HFNC for infants with AVB. We coordinated a multicenter randomized trial during the 2016–2017 respiratory syncytial virus (RSV) epidemic season (TRAMONTANE 2 study, NCT02824744) to assess whether HFNC with a flow rate of 3 L/kg/min would be more effective than 2 L/kg/min.

This trial is now completed and should provide clinicians with helpful evidence on optimal flow in the severe forms of the disease.

Fortunately, randomized controlled trials were also performed with HFNC in mild to moderate—that is, less severe—AVB. One reported efficiency comparable to that of hypertonic saline in treating respiratory distress signs (11), and another reported a significant increase in SpO2 within the first 12 h of management compared with head-box oxygen therapy (12). Very recently, *Lancet* published the results of a single-center open-label trial performed in the John Hunter Hospital in New South Wales (NSW), Australia (13). This study examined whether high-flow warm humidified oxygen (HFWHO)—in other words HFNC—at a maximum flow of 1 L/kg/min and using a 1:1 air-oxygen ratio would reduce the time on oxygen compared with cold wall oxygen 100% at a maximum flow of 2 L per min. This work was actually the first randomized controlled trial comparing HFNC with standard oxygen in a large cohort of infants with AVB admitted to an emergency department and in ward settings. No between-group difference was observed in the survival distributions for time to weaning off oxygen. However, secondary endpoint analysis found clinically important differences in favor of HFNC, which reduced and delayed the occurrence of failure and rescued a majority of infants who were not adequately assisted by standard oxygen therapy.

A notable strength of the study was its inclusion of a standard pediatric observation chart (SPOC), with color-coded trend data for heart rate, respiratory rate, SpO_2 and respiratory distress signs. The SPOC appears to be an original and pragmatic tool for healthcare teams to objectively evaluate patient clinical status and determine the appropriate therapy policy. In the context of AVB, the stability of all indicators in reassuring zones (white/blue) for several hours prompts an oxygen-weaning procedure, whereas the observation of one or several indicators in an alarm zone (yellow/red) signals the need to increase oxygen therapy, to observe the infant more frequently, and even to notify the PICU team. This resource, implemented several years ago by the NSW Ministry of Health, provided the basis for the homogeneous application of the oxygen-weaning schedule in the different clinical units of the study. It was also the cornerstone for defining worsening clinical status and treatment failure. This tool would undoubtedly be a valuable addition to other PICUs and emergency departments for both daily clinical practice and clinical research purposes.

The use of oxygen to resuscitate newborns dates back to 1780 (14), but the titration of FiO_2 according to gestational age and postnatal evolution only came under question in the early 2000s, following experimental and clinical studies demonstrating the toxicity of excessive oxygen administration (15). From a medical viewpoint, Kepreotes *et al.* provided a very important lesson when they reported a reduction in the duration of oxygen therapy in both arms of their study, a result apparently directly related to the standardization in the initiation and weaning of oxygen therapy. Indeed, the authors observed a much shorter duration than that measured in a historical cohort, which nevertheless dates back only to 2007. Beyond the economic considerations, already shown in a previous cost-effectiveness study (16), it is vital to remain very attentive to the risks associated with all treatment administered in the first months of life because it is becoming increasingly evident that early environmental conditions, notably oxidative stress, have an impact on the occurrence of adult diseases (17).

The study also had some limitations, which must of course be considered. The first is related to the definition and homogeneity of the population. The definition of "moderate bronchiolitis" in this report used a high threshold value of SpO_2, that is ≤94%, to justify the need for oxygen therapy, which is far from consensual (18). As a result, the mean baseline SpO_2 in room air in both groups was 96%, suggesting a very modest degree of severity, and this was further indicated by the very short length of stay, on average 2 days. In addition, the enrollment criterion of patients up to 24 months carried the potential risk of including infants with asthma rather than AVB.

The second methodological comment concerns the procedures for oxygen therapy. Oxygen concentrations were clearly different between groups after randomization: HFNC began with FiO_2 equal to 0.6 and standard therapy with "an estimated FiO_2 of 0.3–0.38". Then, the weaning schedules exposed the two groups to unspecified, and probably different, oxygen concentrations, which may have affected the study outcomes. Furthermore, low-flow oxygen administration was not homogeneous in the control group, as some patients received cold but humidified gases and others cold and dry gases, which induces protective bronchoconstrictor responses in normal individuals (19). Last, the possibility of switching an infant from one group to the other in case of failure was unbalanced, as the switch was only possible in the standard oxygen group. This specificity in the study protocol, associated with the inability to conceal the allocated therapy, potentially generated a performance bias.

From a purely scientific viewpoint, the conclusion to be drawn is that HFNC and standard oxygen were both effective in terms of duration of oxygen administration, which implies that early use of HFNC was not able to alter the evolutionary profile of moderate bronchiolitis. HFNC in itself cannot prevent or reduce the pathological changes in the lower airways, dominated by inflammation and plugging, and the favorable effect of this technique on the ventilation/perfusion ratio has not been established (20). The authors' assumption that HFNC would "increase the alveolar surface, improve ventilation-perfusion mismatch, and reduce ventilation inhomogeneities" has poor physiological bases at 1 L/kg, the maximum flow selected by the investigators. In infants with AVB, a linear relation was described between the flow rate, indexed to the patient's weight, and the pharyngeal pressure (1). At 1 L/min, the pressure recordings appeared like a sine wave, negative during inspiration and positive during expiration. A flow rate ≥2 L/kg/min was required to generate CPAP ≥4 cmH_2O (21). The combined measurements of diaphragmatic electrical activity and esophageal pressure swings also suggested the effectiveness of HFNC at the same flow rate to reduce the work of breathing (22). These data underline the value of this support to rapidly offset the patient's inspiratory effort to overcome intrinsic end-expiratory pressure, and to rapidly improve breathing pattern and respiratory distress signs (21).

In spite of the previously mentioned limitations, Kepreotes *et al.* study shows that there is a potential role for HFNC so as to treat mild respiratory failure in the emergency rooms and general wards. From this perspective, the PARIS protocol for a prospective multicenter randomized trial comparing standard oxygen therapy and 2 L/kg/min HFNC in infants with AVB admitted to hospital emergency departments and wards in Australia and New Zealand appears also particularly relevant (23). This study will probably be large enough to convincingly demonstrate that HFNC is a safe and effective primary respiratory support to reduce treatment escalation and unnecessary PICU admissions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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