A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis

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This randomised trial found no evidence of lower rate of escalating respiratory support among patients receiving high-flow oxygen therapy admitted for a first episode of moderate bronchiolitis to the paediatric emergency department https://bit.ly/2xsvqJG

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ABSTRACT

Background: The objective was to determine whether high-flow nasal cannula (HFNC), a promising respiratory support in infant bronchiolitis, could reduce the proportion of treatment failure requiring escalation of care.

Methods: In this randomised controlled trial, we assigned infants aged <6 months who had moderate bronchiolitis to receive either HFNC at 3 $L \cdot kg^{-1} \cdot min^{-1}$ or standard oxygen therapy. Crossover was not allowed. The primary outcome was the proportion of patients in treatment failure requiring escalation of care (mostly noninvasive ventilation) within 7 days following randomisation. Secondary outcomes included rates of transfer to the paediatric intensive care unit (PICU), oxygen, number of artificial nutritional support-free days and adverse events.

Results: The analyses included 268 patients among the 2621 infants assessed for inclusion during two consecutive seasons in 17 French paediatric emergency departments. The percentage of infants in treatment failure was 14% (19 out of 133) in the study group, compared to 20% (27 out of 135) in the control group (OR 0.66, 95% CI 0.35–1.26; p=0.21). HFNC did not reduce the risk of admission to PICU (21 (15%) out of 133 in the study group *versus* 26 (19%) out of 135 in the control group) (OR 0.78, 95% CI 0.41–1.41; p=0.45). The main reason for treatment failure was the worsening of modified Wood clinical asthma score (m-WCAS). Short-term assessment of respiratory status showed a significant difference for m-WCAS and respiratory rate in favour of HFNC. Three pneumothoraces were reported in the study group.

Conclusions: In patients with moderate bronchiolitis, there was no evidence of lower rate of escalating respiratory support among those receiving HFNC therapy.

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Introduction

Acute viral bronchiolitis remains the leading cause of acute respiratory failure in infants in developed countries [1–3]. As stated by both the American Academy of Pediatrics and related UK guidelines, treatment is mainly supportive and includes monitoring, low-flow oxygen therapy, hydration or nutritional support [4, 5]. This approach remains the cornerstone of standard care, and thus far, no specific medical therapy has proven beneficial [6]. Over the past decade, high-flow nasal cannula (HFNC) has emerged as a promising method to provide respiratory support in children with severe bronchiolitis either during interhospital transfer or in the paediatric intensive care unit (PICU) [7–11]. Oxygen delivery with HFNC allows for the administration of a heated and humidified blend of air and oxygen at various flow rates $\geqslant 2$ L·min^{-1} that can be matched to the patient's inspiratory flow. Various physiological effects have been demonstrated including flow rate-dependent distending pressure, decreased airway resistance and work of breathing, as well as dead-space washout. Nevertheless, no current evidence suggests that early or pre-emptive support with HFNC in either paediatric emergency departments (PEDs) or general wards is superior to standard care (*e.g.* low-flow oxygen therapy) for reducing the risk of acute respiratory failure leading to escalating respiratory support, which is mainly provided by nasal continuous positive airway pressure (nCPAP) [2, 12, 13]. Thus far, only two prospective randomised controlled trials (RCTs) have compared HFNC with low-flow oxygen therapy in patients with less severe bronchiolitis admitted to general wards, but both failed to clearly demonstrate a reduction in the length of oxygen therapy or in the proportion of patients transferred to the PICU [14, 15]. Other issues regarding high-flow therapy include the potential for rapid deterioration outside the PICU in intermediate-level care (PEDs and wards), as well as the method's cost-effectiveness or the potential costs associated with overuse. Recent UK guidelines suggest that an RCT comparing HFNC and standard supplemental oxygen would be beneficial to address these questions [4]. Therefore, we performed an RCT evaluating high- *versus* low-flow oxygen therapy, including standard care, in infants with moderate-severity bronchiolitis (defined as a modified Wood clinical asthma score (m-WCAS) >2 and requiring supplemental oxygen) admitted to PEDs and subsequently general ward units. We aimed to determine whether HFNC in this setting could reduce the rate of treatment failure requiring escalation of care.

Methods

Trial design

This multicentre open-label RCT was performed in the emergency departments and general paediatric wards of 17 hospitals (a paediatric hospital network) in the southern and eastern suburbs of Paris, including 13 nontertiary regional/metropolitan hospitals. Only one of these centres (Bicêtre hospital) had access to an on-site PICU, while three had an on-site intermediate level unit. Three of the recruiting centres had previous experience with HFNC before starting the study.

Group education sessions with attending physicians, nurses, and junior medical officers were conducted in each recruiting centre before the start of the study. This training involved a planned visit to the emergency department and with ward staff by the lead investigator (PD) and clinical research associates (Marylise Adechian, Domitille Molinari) to present specific examples of HFNC drawn from video recordings. Clinicians were specifically trained in eligibility criteria involving the m-WCAS score and how to respond to treatment failure during the study (supplementary table E1).

The study protocol was approved by the Paris-Ile de France XI ethics committee (2016-A00568-43). Written authorisation was obtained from both parents of each patient after appropriate information was provided.

Infants with moderate bronchiolitis who were seen at participating PEDs were eligible for the study. The inclusion criteria were as follows: a first episode of hospitalisation for bronchiolitis (as defined by

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American Academy of Pediatrics clinical recommendations) in infants aged 7 days to 6 months with one episode of pulse oximetry-measured oxygen saturation (S_{pO_2}) <95% while on room air at any time before randomisation and m-WCAS between 2 and 5 at inclusion [7, 14, 16]. The agreement of at least one parent or legal guardian to participate in biomedical research, as well as affiliation with the public healthcare system (beneficiary or entitled), was required. Infants were not eligible if they had any of the following: urgent need for mechanical ventilation support either by nCPAP or the endotracheal route, a severe form of bronchiolitis defined by m-WCAS >5 and the requirement for noninvasive ventilation, uncorrected cyanotic heart disease, innate immune deficiency, craniofacial malformation, congenital stridor and tracheotomy.

Included patients were randomly assigned to the control or HFNC group using an electronic system-based randomisation method and stratified according to centre (using a 1:1 allocation sequence ratio by two to four random blocks) within 48 h after admission (https://cleanweb-production3.aphp.fr). They received either standard oxygen therapy (up to 2 L·min^{-1} to maintain S_{pO_2} at ⩾94%) (control group) or HFNC therapy delivered *via* an Airvo 2 turbine through an Optiflow junior infant size cannula (OPT316) (Fisher & Paykel Healthcare, Auckland, New Zealand) (setting at 3 L·kg^{-1}·min^{-1}, min 7 to max 20 L·min^{-1}, inspiratory oxygen fraction (F_{iO_2}) adjusted to obtain a similar S_{pO_2} target) (HFNC group). Crossover was not allowed. All patients received similar standard care at the discretion of the attending physician, but physiotherapy, steroids and inhaled bronchodilator drugs were discouraged.

Treatment failure criteria indicating release from the study were defined as follows: at least one of F_{iO_2} requirement on HFNC >40% (HFNC group) or nasal flow oxygen >2 L·min^{-1} (control group) in order to maintain S_{pO_2} ⩾94%, elevated m-WCAS score (*i.e.* by ⩾1 point) at hour 6 compared to baseline and/or any scores >5, refractory apnoea episodes (>3 events·h^{-1}) and/or increasing arterial carbon dioxide tension compared to baseline and/or >60 mmHg at hour 6.

In the HFNC group, the use of a pacifier was recommended to reduce mouth leaks. Weaning procedures were protocolised by reducing the flow rate by 2 L·min^{-1} increments every 8 h starting at hour 12 and when F_{iO_2} could be reduced to ⩽25%.

The Airvo 2 turbine, tubing, heated humidifiers, and prong cannulas (*i.e.* consumable materials) were provided to the participating centres during the study period by Fisher & Paykel Healthcare, which had no other involvement in the study.

Outcomes

The primary end-point was the proportion of patients in each group that experienced treatment failure requiring escalating treatment within 7 days following randomisation. Escalating treatment was defined as the application of noninvasive or invasive ventilation in the overall population or the use of HFNC in the control group.

Secondary outcomes included the rates of transfer to the PICU among patients in treatment failure (either on-site or an intensive care unit referral centre), an assessment of short-term respiratory status (at hours 1, 6 and 12), paediatric general ward unit length-of-stay, oxygen support-free days and artificial nutritional support-free days.

Statistical analysis

The trial was designed to evaluate the superiority of HFNC in comparison to the standard of care in terms of failure rate. For the intention-to-treat analysis, the following assumptions were made: a 30% event rate in the control group and a 15% event rate in the HFNC group, providing a relative risk reduction with HFNC of ⩾50%. This assumption was based on a literature analysis [10, 17–19]. Assuming a 15% rate of patients enrolling despite not being eligible for randomisation, as well as consent withdrawals or loss to follow-up for the primary end-point, we estimated that 140 patients per group would give the study ⩾80% power to demonstrate the superiority of HFNC (risk α=5% and β=20%). We did not plan an interim analysis.

Our primary analysis was conducted using an intention-to-treat approach, and it therefore included all randomised infants. Baseline characteristics of the patients in each group were reported using frequency distributions and descriptive statistics, including measures of central tendency and dispersion. Between-group differences were analysed using a t-test or Wilcoxon rank-sum test for continuous variables or a Chi-squared test for categorical variables, as appropriate, and are reported as estimated median differences (Hodges–Lehman estimate) or odds ratios with 95% confidence intervals. Kaplan–Meier curves were plotted to assess the time from enrolment to failure (*i.e.* requiring escalation of treatment) and were compared using a log-rank test. All analyses were conducted using Stata version 14 software (StataCorp,

College Station, TX, USA) in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. p<0.05 was considered statistically significant.

Results

Patient characteristics

From November 1, 2016 through March 31, 2017 and from October 1 to November 15, 2017, a total of 2621 patients admitted for bronchiolitis to the 17 PEDs of the participating centres were screened, of whom 271 underwent randomisation. Data on the primary outcome were available for 268 of these patients for the intention-to-treat analysis (figure 1). Demographics and clinical characteristics were similar at inclusion except for a slightly lower mean m-WCAS score value in the control group (p=0.028) (table 1). Given that several patients were excluded after randomisation (figure 1), inclusions were prematurely ended at the discretion of the steering committee once the prespecified sample size was reached.

Primary outcome

HFNC did not improve the primary outcome among the 268 patients included in the intention-to-treat analysis. Failure occurred in 19 (14%) out of 133 patients in the HFNC group and 27 (20%) out of 135 patients in the standard oxygen therapy group (including nine patients treated with high-flow nasal cannula in an intensive care unit (ICU)) at 7 days after randomisation (table 2, figure 2). No patient underwent invasive ventilation during the study. The main reason for treatment failure was worsening m-WCAS score in the first 6 h following randomisation. This complication accounted for 12 and 20 failures in the HFNC and control groups, respectively, and did not differ significantly between the two groups (supplementary table E2). Severity at the time of failure was evidenced by mean m-WCAS score and transcutaneous carbon dioxide tension (P_{tCO_2}) values. However, except for mean P_{tCO_2} value, which was significantly higher in the control group compared to the HFNC group, we did not find any between-group differences for oxygen requirement or apnoea events (supplementary table E2).

Secondary outcomes

Similarly, HFNC did not reduce the risk of admission to the ICU (neither on-site nor referral tertiary PICUs) (21 (15%) in the HFNC group *versus* 26 (19%) in the control group (p=0.45)) (table 2). The mean

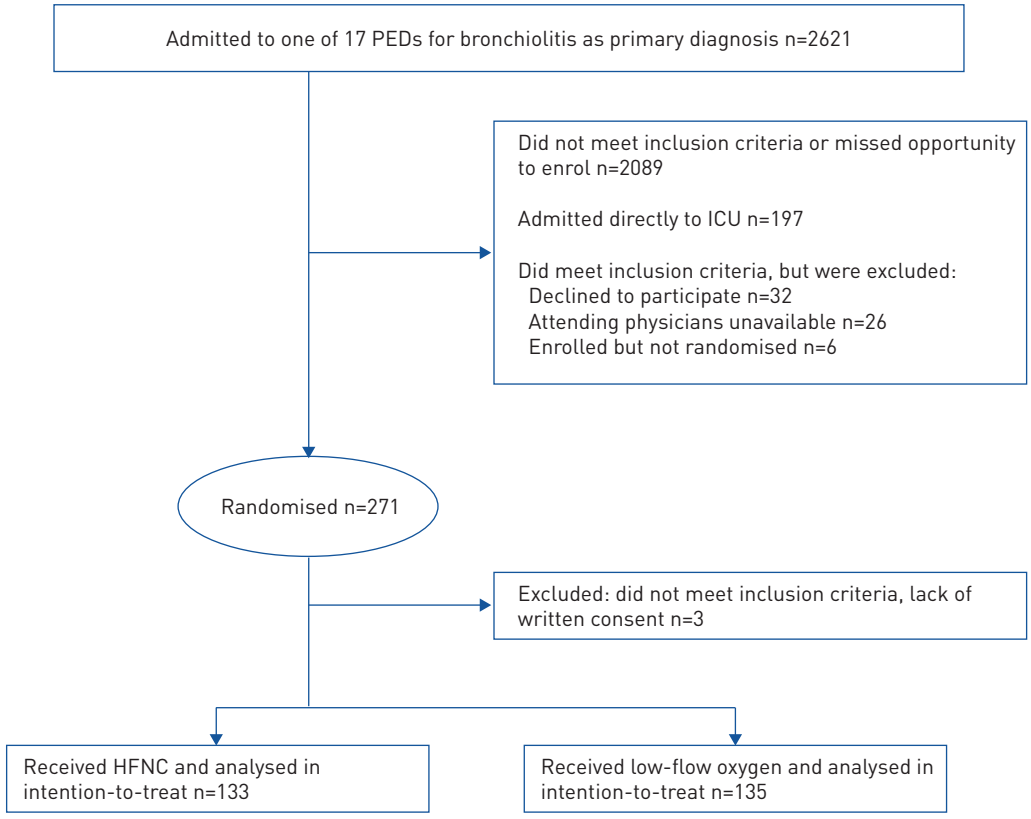


FIGURE 1 Eligibility, randomisation and follow-up of the study participants. PED: paediatric emergency department; ICU: intensive care unit; HFNC: high-flow nasal cannula.

TABLE 1 Patient characteristics and respiratory variables according to group at randomisation (before any study intervention)

	HFNC	Control
Patients	133	135
Characteristics		
Age days	68±48	65±46
Weight kg	5.1±1.5	4.9±1.4
Female	52 (39)	65 (48)
Gestational age weeks	38±2	38±2
Premature birth (<37 weeks)	16 (12)	16 (11)
Clinical variable		
Duration of symptoms before randomisation days	3.3±2.1	3.1±2.2
Temperature °C	37.2±0.6	37.2±0.5
Respiratory rate bpm	53±13	55±14
Heart rate bpm	156±18	154±18
S_{pO_2} % in room air	90±3	90±3
m-WCAS	3.3±0.8	3.1±0.7
P_{tCO_2} [#] mmHg	50±11	50±10
pH	7.34±0.07	7.33±0.05
Viral cause		
Number tested	103	105
RSV status	85 (82)	87 (82)
Other	5 (4)	1 (1)

Data are presented as n, mean±SD or n (%). HFNC: high-flow nasal cannula; S_{pO_2}: pulse oximetry-measured oxygen saturation; m-WCAS: modified Wood clinical asthma score; P_{tCO_2}: transcutaneous carbon dioxide tension; RSV: respiratory syncytial virus. [#]: available in 49 and 43 patients in HFNC and control groups, respectively.

length of oxygen therapy (defined by the use of >21% F_{iO_2} in the HFNC group or nasal oxygen requirement in the control group) until discharge home or ICU-level admission was lower in the HFNC compared to control group (p=0.001). The short-term assessment of respiratory status is displayed in table 3 and did not show significant differences, except for the m-WCAS score at hour 1 and respiratory frequency at hours 6 and 12, in favour of the HFNC group.

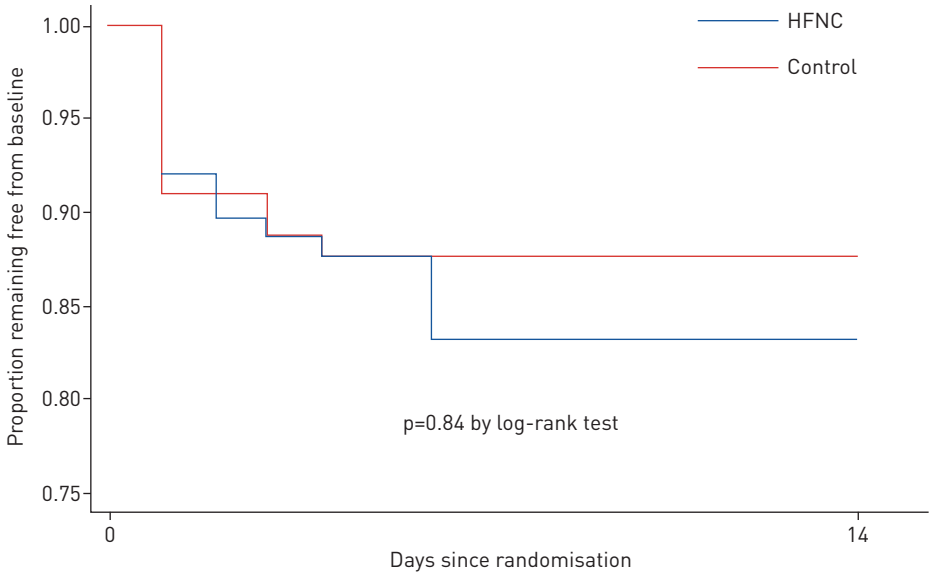
Safety

All patients tolerated high-flow oxygen therapy well. None reported nasal mucosa or skin trauma. However, three pneumothoraces, including two cases of pneumomediastinum, occurred in patients randomised to the HFNC group; these both showed spontaneous favourable evolution without the need for chest drainage. The attending physicians suggested that the use of HFNC was probably or definitely related to these air leak events. No life-threatening serious adverse complications were reported, including no instances of endotracheal intubation or cardiac arrest.

TABLE 2 Primary and secondary outcomes according to group

	HFNC	Control	OR (95% CI)	Mean difference (95% CI)
Patients n	133	135		
Primary outcome (escalating within 7 days)[#]	19 (14)	27 (20)	0.66 (0.35–1.26)	
Secondary outcome				
Failure requiring ICU transfer within 7 days (ICU on-site or tertiary care)	21 (15)[§]	26 (19)[f]	0.78 (0.41–1.41)	
Length of nutritional support days[¶]	2.9±2.1	2.4±2.2		0.50 (−0.04–1.04)
Length of oxygen support days[+]	1.7±1.7	2.5±2		−0.80 (−1.2–−0.3)
Length of stay on general ward unit days[¶]	4.4±2.4	3.8±2.7		0.6 (−0.04–1.2)

Data are presented as n (%) or mean±SD of patients, unless otherwise stated. HFNC: high-flow nasal cannula; ICU: intensive care unit. [#]: noninvasive ventilation (NIV) or HFNC support in control group and NIV support in HFNC group in case of failure; [¶]: until discharge at home or ICU-level admission; [+]: inspiratory oxygen fraction >21% (HFNC group) or nasal oxygen requirement (control group) until discharge at home or ICU-level admission; [§]: two additional patients in study group who failed were kept on HFNC during their paediatric ICU stay; [f]: one patient in control group who failed and escalated on HFNC was kept on the paediatric general ward.



At risk n

HFNC	133	125	125	115	110	88	62	38	22	13	6	5
Control	135	122	122	105	88	69	51	38	23	11	6	5

FIGURE 2 Kaplan–Meier plot of the proportion of moderate bronchiolitis patients remaining free of escalating treatment (defined by noninvasive ventilation or high-flow nasal cannula (HFNC) in control group and noninvasive ventilation in HFNC group only) since randomisation, according to group.

TABLE 3 Physiological variables and modified Wood clinical asthma score (m-WCAS) at 1 h and after 6 and 12 h after randomisation according to group

	HFNC	Control	Mean difference (95% CI)	p-value
Subjects n	133	135		
1 h				
f_R breaths·min^{-1}	46±13	50±13	−4. (−7.5–−0.9)	0.01
HR bpm	151±18	151±16	0.3 (−3.9–4.6)	NS
S_{pO_2} %	97±2	97±3	0.02 (−0.6–0.7)	NS
F_{iO_2}[#] or oxygen flow rate[¶]	25±5%	0.5±0.4 L·min^{-1}		NA
m-WCAS change	−0.098±0.22	−0.036±0.23	−0.06 (−0.12–−0.004)	<0.01
Apnoea events	1	1		ND
6 h				
f_R breaths·min^{-1}	45±13	49±15	−3.6 (−7.2–0.004)	0.05
HR bpm	152±17	151±18	1.2 (−3.1–5.6)	NS
S_{pO_2} %	97±2	97±2	−0.04 (−0.6–0 .5)	NS
P_{tCO_2} mmHg	44 ±7	48±10	−3.6 (−8.5–1.2)	NS
F_{iO_2}[#] or oxygen flow rate[¶]	26±6%	0.5±0.3 L·min^{-1}		NA
m-WCAS change	−0.16±0.35	0.11±0.31	−0.05 (−0.1–0.03)	NS
Apnoea events	0	0		ND
12 h				
f_R breaths·min^{-1}	42±13	47±14	−4.8 (−8.3–−1.2)	0.01
HR bpm	146±18	145±18	1.5 (−3.1–6.1)	NS
S_{pO_2} %	97±2	97±2	−0.3 (−0.9–0.2)	NS
F_{iO_2}[#] or oxygen flow rate[¶]	25±5%	0.5±0.4 L·min^{-1}		NA
m-WCAS change	−0.23±0.31	−0.15±0.38	−0.07 (−0.1–0.02)	NS

Data are presented as n, mean±SD or n (%), unless otherwise stated. HFNC: high-flow nasal cannula; f_R: respiratory frequency; HR: heart rate; S_{pO_2}: pulse oximetry-measured oxygen saturation; F_{iO_2}: inspiratory oxygen fraction; P_{tCO_2}: transcutaneous carbon dioxide tension; NS: nonsignificant; NA: not applicable; ND: not determined. [#]: HFNC group; [¶]: control group.

Discussion

In this multicentre randomised controlled trial involving infants with moderate bronchiolitis admitted to PEDs or inpatient wards, there was no evidence of a lower rate of failure leading to noninvasive ventilation support in patients receiving high-flow oxygen therapy compared to the control group. There was no significant between-group difference in the rate of ICU admission, while a marginal benefit of HFNC was observed for short-term respiratory parameters or length of oxygen therapy. However, in the HFNC group, three device-associated air leak syndromes were reported.

Our findings are partially supported by the results of two recent randomised trials, which found no difference in ICU admission rates between the two strategies [14, 15].

Regarding the observation that the time to wean off oxygen favoured the HFNC group, this difference may be considered irrelevant, consistent with the negative results reported in the two previously published RCTs (*i.e.* no significant difference in length of oxygen support between the HFNC and control group).

The first single-centre RCT was designed to demonstrate a reduction in the time to wean off oxygen. No difference was found between the two groups for the primary outcome or in the proportion of patients transferred to the PICU. However, although the percentage of children who experienced treatment failure was lower in the HFNC group (14% compared to 33% in the standard therapy group; p=0.0016), the study was underpowered for this secondary end-point. Finally, the relatively low flow setting of 1 $L{\cdot}kg^{-1}{\cdot}min^{-1}$ in the HFNC group, the low mean m-WCAS score (compared to our data) and the rate of crossover in the standard group raised concerns about generalising these findings to other wards [14]. The crossover rate makes it difficult to draw definitive conclusions regarding the usefulness of high-flow oxygen therapy in very low-severity forms of bronchiolitis. The second study, a large multicentre RCT, aimed to compare HFNC (flow setting of 2 $L{\cdot}kg^{-1}{\cdot}min^{-1}$) to standard therapy with the primary outcome as the rate of escalating therapy, which was defined as a heterogeneous composite failure criterion including meeting an early warning sign-driven protocol, admission to the ICU and/or crossover to HFNC in the control patients. Despite a significantly higher rate of failure-free days in favour of the HFNC group, neither the proportion of patients admitted to the ICU nor the number of oxygen-free days were found to be significantly different. Moreover, the number of patients who underwent noninvasive ventilation in the failure group was unknown [15]. However, the clinical benefit highlighted in these two RCTs (*i.e.* the proportion of failure-free days in favour of HFNC) is consistent with our observed short-term improvements in respiratory rate, m-WCAS score or mean P_{tCO_2} at failure in the HFNC group. These findings are consistent with an extensive literature focused on the physiological benefits of HFNC in infants and adults, which stress the benefit of reduced work of breathing.

Finally, several concerns have been noted regarding cost-effectiveness in terms of the high rate of crossover in the control group, as this indicates bias of the attending physicians toward HFNC as a beneficial therapy at the time of crossover, even though the evidence for the benefit of HFNC in "moderate" bronchiolitis (*i.e.* all patients admitted to the ward and requiring oxygen to target a S_{pO_2} level of 92–98%) remains to be established [20].

It is worth noting that our ~10% inclusion rate of total infants admitted to the PED with bronchiolitis as a primary diagnosis is quite similar to that in the study by Franklin *et al.* [15]. Interestingly, our failure rates in the HFNC and control groups (20% and 14%, respectively) are comparable to their subgroup of patients in recruiting institutions with an on-site PICU. However, neither the inclusion and/or failure criteria nor the primary end-point were similar between the two studies, which makes these comparisons much more difficult, especially because our pragmatic "real-world" trial was not designed to explain these differences.

Indeed, our study included infants aged <6 months during two consecutive winter epidemic outbreaks in order to decrease the risk of including infant asthma patients and to target subgroups at higher risk for admission to the ICU, in contrast to previous RCTs [1, 2, 21, 22]. Furthermore, we chose an escalating respiratory support requirement (mainly with nCPAP) as a pragmatic judgment criterion because it is currently considered standard first-line treatment for severe cases admitted to the PICU in most developed countries, despite a lack of evidence from RCTs [4, 7, 12]. Indeed, we and others suggest that avoiding admission to the PICU or noninvasive support are more relevant end-points, as both are associated with the PICU seasonal burden, substantial complications and higher costs [23]. Finally, some features are likely to reduce interpretation bias, including the fact that the design did not allow crossover between the groups and the absence of a PICU in all but one recruiting centre.

Although the study did not use a crossover design, 10 infants from the control group were escalated to HFNC (nine in the ICU; one remained in the ward) (table 2). Once the patient met the failure criteria in each group, indicating release from the study, physicians were not able to both escalate and remain in the randomisation arm, meaning that the patient had to be admitted to intermediate level care or the ICU. It should be noted that the PICU team caring for infants in the failure group was not involved in the study design. Thus, the

choice to escalate support was entirely at the entire discretion of the paediatric intensivist, which is why several patients who failed in the control arm received support with HFNC after their ICU admission.

We chose a 3 $L \cdot kg^{-1} \cdot min^{-1}$ flow rate in our study given that a previous physiological study suggested that maintaining a pharyngeal pressure-to-flow relationship above 2 $L \cdot kg^{-1} \cdot min^{-1}$ helps reduce work of breathing [24]. Moreover, a similar flow rate close to or above 3 $L \cdot kg^{-1} \cdot min^{-1}$ has also been used in two other RCTs that included premature newborns after extubation [25, 26]. We could not rule out worsened work of breathing in some patients due to individual excess inflow rate and/or discomfort, which would mask a potential benefit in the HFNC group. This is consistent with a recent RCT, which indeed suggested that a 3 $L \cdot kg^{-1} \cdot min^{-1}$ flow rate did not reduce the risk of treatment failure compared to the 2 $L \cdot kg^{-1} \cdot min^{-1}$ arm in severe bronchiolitis [16]. However, the short-term improvement in respiratory rate or m-WCAS score in the HFNC group is consistent with previous literature evaluating the physiological benefits of HFNC in infants and adults [24, 27–29].

Serious, unexpected adverse events encountered in the HFNC group are a matter of concern, especially because potentially serious air-leak syndromes have previously been reported with high-flow oxygen therapy devices [19, 30]. We propose several hypotheses, including nasal prong sizes that are unable to provide sufficient nostril leakage in some patients (unfortunately, a fixed size apparatus was used for the entire study group), incorrect pacifier use and/or an excessive fixed-flow rate setting at 3 $L \cdot kg^{-1} \cdot min^{-1}$ in our study.

The limitations and weaknesses of our study include the fact that the median m-WCAS score was slightly but significantly higher at randomisation in the HFNC group, indicating that some inclusion bias cannot be ruled out, though it should be emphasised that this significant difference was not clinically relevant. Given the substantial difference in a physician deciding to escalate to HFNC (especially if the patient is to remain in the ward) *versus* escalating to NIV, we cannot rule out an evaluation bias regarding the inescapable nonblinded design features, as severity at the time of failure could be lower in the control group despite a lack of evidence (supplementary table E2). In the same way, not knowing the exact time from admission to randomisation make the comparison more challenging. Another potential interpretation bias could be the S_{pO_2} target chosen for oxygen therapy and failure criteria, given that our chosen value is substantially higher than the 90% threshold listed in AAP guidelines threshold and subsequently recommended by the WHO. The translatability of these results remains, and our findings are likely not generalisable to most centres [31]. However, it could be argued that the number patients who failed in both groups due to hypoxaemia was well balanced (supplementary table E2) and similar to Franklin *et al.*'s [15] study results using a similar oxygen therapy threshold. The failure rate observed in the control group was lower than expected (20%), and thus the number of patients included in the study did not allow for detection of a minimum difference of 60% with a similar power. This combination of factors puts the study at risk of being underpowered. Attending physicians were not always available 24 h/7 days a week, which may have limited the representativeness of our population by reducing the number of enrolment opportunities.

In conclusion, the results of our study do not support the pre-emptive and routine use of respiratory support by HFNC at a setting of 3 $L \cdot kg^{-1} \cdot min^{-1}$ in patients admitted to a PED and then onward for moderate viral bronchiolitis. Although HFNC may not be best used as a general practice, the criteria for its use in paediatric wards should be further defined.

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