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Early View

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A Randomized Trial of High-Flow Nasal Cannula in Infants with Moderate Bronchiolitis.

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Keys words: bronchiolitis, infant, oxygen therapy, high-flow nasal cannula.

Take home message: This randomized 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 pediatric emergency department.

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 RCT, we assigned infants younger than 6 months who had moderate bronchiolitis to receive either HFNC at 3l/kg/min or standard oxygen therapy. Cross-over was not allowed. The primary outcome was the proportion of patient in treatment failure requiring escalation of care (mostly non-invasive ventilation) within 7-days following randomization. Secondary outcome included rates of transfer in PICU, oxygen and nutritional-support length of days and adverse events.

Results: The analyses included 268 patients among the 2621 infants assessed for inclusion during 2 consecutive seasons in 17 French pediatric emergency departments. The percentage of infants in treatment failure was 14% (19 of 133) in the study group, compared to 20% (27 of 135) in the control group (OR 0.66; CI 95% 0.35-1.26, p=0.21). HFNC did not reduce the risk of admission in PICU (21 of 133 in the study group (15%) versus 26 of 135 in the control group (19%))(OR 0.78; CI 95% 0.41- 1.41, p = .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 favor 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.

Acute viral bronchiolitis remains the leading cause of acute respiratory failure in infants in developed countries (1)(2)(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 last 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 PICU (7)(8)(9)(10)(11). Oxygen delivery with high-flow nasal cannula allows for the administration of a heated and humidified blend of air and oxygen at various flow rates exceeding ≥2 L/min 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 wash-out. Nevertheless, no current evidence suggests that early or preemptive support with HFNC in either pediatric 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 randomized controlled trials have compared high-flow nasal cannula 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. UK guidelines recently suggested that a randomized control study (RCT) comparing HFNC and standard supplemental oxygen would be beneficial to address these questions (4). Therefore, we performed a randomized controlled trial evaluating high- versus low-flow oxygen therapy, including standard care, in infants with moderate severity bronchiolitis (defined as a modified WCAS >2 and requiring supplemental oxygen) admitted to PEDs and subsequently general ward units. We aimed to determine whether in this setting HFNC could reduce the rate of treatment failure requiring escalation of care.

Methods

Trial design

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

Group education sessions conducted in each recruiting center with attending physicians, nurses, and junior medical officers were before the start of the study. This training involved a planned visit to the emergency department and with ward staff by the lead investigator (P Durand) and clinical research associates (M Adechian, D Molinari) to present specific examples of HFNC drawn from video recordings. Clinicians were specifically trained in eligibility criteria involving the modified Wood clinical asthma score (m-WCAS score) and how to respond to treatment failure during the study (see eTable 1 in the online supplement).

The study protocol was approved by the "Paris-Ile de France XI" ethics committee (2016-A00568-43). Written authorization 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 hospitalization for bronchiolitis (as defined by American Academy of Pediatrics clinical recommendations) in infants aged 7 days to 6 months with one episode of pulse oximetry-measured SpO2 lower than 95% while on room air at any time before randomization and a modified Wood clinical asthma score (m-WCAS) between 2 and 5 at inclusion (14)(7)(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 a m-WCAS >5 and the requirement for non-invasive 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 randomization method and stratified according to center (using a 1:1 allocation sequence ratio by 2 to 4 random block) within 48 hours after admission (https://cleanweb.aphp.fr/Ctms-02/portal). They received either standard oxygen therapy (up

to 2 L/min to maintain SpO2 at 94% or higher) (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/min, min 7 to max 20 L/min, FiO2 adjusted to obtain a similar SpO2 target) (HFNC group). Cross-over 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): FiO2 requirement on HFNC greater than 40% (HFNC group) or nasal flow oxygen above 2 L/min (control group) in order to maintain SpO2 ≥94%, elevated m-WCAS score (i.e., by 1 point or more) at hour 6 compared to baseline and/or any scores higher than 5, refractory apnea episodes (more than 3 per hour) and or increasing PaCO2 compared to baseline and/or above 60 mmHg at hour 6.

In the HFNC group, the use of a pacifier was recommended to reduce mouth leaks. Weaning procedures were protocolized by reducing the flow rate by 2 L/min increments every 8 hours starting at hour 12 and when FiO2 could be reduced to 25% or less.

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

Outcomes

The primary endpoint was the proportion of patients in each group that experienced treatment failure requiring escalating treatment within 7 days following randomization. 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 ICU referral center), an assessment of short-term respiratory status (at hours 1, 6 and 12), pediatric 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 at least 50%. This assumption was based on a literature analysis (10)(17)(18)(19). Assuming a 15% rate of patients enrolling despite not being eligible for randomization, as well as consent withdrawals or loss to follow-up for the primary endpoint, we estimated that 140 patients per group would give the study at least 80% power to demonstrate the superiority of HFNC (risk alpha=5% and beta=20%). We did not plan an interim analysis.

Our primary analysis was conducted using an intent-to-treat approach, and it therefore included all randomized 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 analyzed with a Student's t-test or Wilcoxon rank-sum test for continuous variables or a chi-square 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 enrollment to failure (i.e., requiring escalating treatment) and were compared using a log-rank test. All analyses were conducted using Stata version 14 software (StataCorp) in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From November 1st, 2016 through March 31th, 2017 and from October 1st to November 15th, 2017, a total of 2,621 patients admitted for bronchiolitis to the seventeen PEDs of the participating centers were screened, among whom 271 underwent randomization. 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 randomization (Figure 1), inclusions were prematurely ended at the discretion of the steering committee once the pre-specified 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 of 133 patients (14%) in the HFNC group and 27 of

135 (20%) patients in the standard oxygen therapy group (including 9 patients treated with high-flow nasal cannula in an ICU) at 7 days after randomization (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 hours following randomization. This complication accounted for 12 and 20 failures in the HFNC and control groups, respectively, and did not significantly differ between the two groups (see the eTable 2 online supplement). Severity at the time of failure was evidenced by mean m-WCAS score and PtCO2 values. However, except for mean PtCO2 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 apnea events (see the eTable 2 online supplement).

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 length of oxygen therapy (defined by the use of >21% FiO2 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 RR at hours 6 and 12, in favor 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 randomized to the HFNC group; these both showed spontaneous favorable evolution without the need for chest drainage. The attending physicians suggested that the use of HFNC was likely 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.

Discussion

In this multicenter, randomized controlled trial involving infants with moderate bronchiolitis admitted to PEDs or inpatient wards, there was no evidence for 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 randomized 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 favored 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-center 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 endpoint. Finally, the relatively low flow setting of 1 L.kg.min-1 in the HFNC group, the low mean m-WCAS score (compared to our data) and the rate of crossing over in the standard group raised concerns about generalizing 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 multicenter RCT, aimed to compare HFNC (flow setting of 2 L.kg.min-1) to standard therapy with the primary outcome as the rate of escalating therapy, which was defined as a heterogeneous composite failure criteria 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 favor 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 favor of HFNC) is consistent with our observed short-term improvements in respiratory rate, m-WCAS score or mean PtCO2 at failure in the HFNC group. These findings are also 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 SpO2 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 of Franklin's study (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 endpoint 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 younger than 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 (2)(1)(21)(22). Furthermore, we chose an escalating respiratory support requirement (mainly with nCPAP) as a pragmatic judgment criteria 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 pediatric intensive care unit or NIV support are more relevant endpoints, 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 center.

Although the study did not use a crossover design, 10 infants from the control group were escalated to HFNC (9 in the ICU and 1 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 randomization 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 pediatric 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/kg/min flow rate in our study given that a previous physiological study suggested that maintaining a pharyngeal pressure-to-flow relationship above 2 L/kg/min helps reduce work of breathing (24). Moreover, a similar flow rate close to or above 3 L/kg/min 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/kg/min flow rate did not reduce the risk of treatment failure compared to the 2 L/kg/min 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 (27)(28)(24)(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/kg/min 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 randomization in the HFNC group, indicating that some inclusion bias cannot be ruled out, though it should be emphasized 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) vs. escalating to NIV, we cannot rule out an evaluation bias regarding the inescapable non-blinded design features, as severity at the time of failure could be lower in the control group despite a lack of evidence (eTable 2). In the same way, not knowing the exact time from admission to randomization make the comparison more challenging. Another potential interpretation bias could be the SpO2 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 generalizable to most centers (31). However, one could argue that the number patients who failed in both groups due to hypoxemia was well balanced (eTable 2 online supplement) and similar to Franklin's 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 twenty-four hours/seven 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 preemptive and routine use of respiratory support by HFNC at a setting of 3 L/kg/min 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 pediatric wards should be further defined.

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Figure 1. Eligibility, randomization, and follow-up of the study participants.

Figure 2. Kaplan-Meier plot of the Proportion of moderate bronchiolitis remaining free of escalating treatment (defining by non-invasive ventilation or HFNC in control group and non-invasive ventilation in HFNC group only) since Randomization according to Group.

Table 1. Patient characteristics and respiratory variables according to group at randomization (before any study intervention).

Table 2. Primary and secondary outcomes according to group.

Table 3. Physiologic variables and m-WCAS score at 1, 6 and 12-hours after randomization according to study group.

Table 1. Patient Characteristics and Respiratory Variables according to Group at Randomization (Before Any Study Intervention) ¶

Characteristics	HFNC group (N=133)	Control group (N=135)
Age**,** Mean (SD)-days	68 ± 48	65±46
Weight**,** Mean (SD)-kg	5.1 ±1.5	4.9±1.4
Female sex-no.(%)	52 (39)	65 (48)
Gestational age, Mean (SD)-weeks	38± 2	38±2
- premature birth (<37 weeks), no.(%)	16 (12)	16 (11)
Clinical variable, Mean (SD)		
Duration of symptoms before randomization, Mean (SD)-days	3.3± 2.1	3.1±2.2
Temperature, Mean (SD) -°C	37.2±0.6	37.2±0.5
Respiratory rate, Mean (SD) - bpm	53±13	55±14
Heart rate, Mean (SD)-bpm	156 ±18	154±18
SpO2, Mean (SD)-% in room air	90 ± 3	90±3
m-WSCA score, Mean (SD)	3.3 ±0.8	3.1±0.7
P(t)CO2, Mean (SD)-mmHg#	50±11	50±10
pH, Mean (SD)	7.34±0.07	7.33±0.05
Viral cause-no./total no.(%)		
Number tested, no	103	105
RVS status, no. (%)	85 (82)	87 (82)
others	5 (4)	1 (1)

¶ datas are presented as number (percentage) or mean±SD of patients

available in 49 and 43 patients in HFNC and Control group respectively.

HFNC denote high-flow nasal cannula, ND denote not determined, m-WSCA score denote modified-Wood clinical asthma score, P(t)CO2 transcutaneous or PaCO2 value.

Table 2. Primary and Secondary Outcomes according to Group¶

Characteristics	HFNC group (N=133)	Control group (N=135)	Odds ratios or Mean difference (95% CI)[#]
Primary Outcome: - escalating within day-7- no.(%)*	19 (14)	27 (20)	0.66 [0.35; 1.26]
Secondary outcome:			
- failure requiring ICU transferred within day-7 (ICU-on-site or tertiary care)- no.(%)	21 (15)[§]	26 (19)[£]	0.78 [0.41; 1.41]
- length of nutritionnal support-days †	2.9±2.1	2.4±2.2	0.50 (-0.04 to 1.04)
- length of oxygen support-days‡	1.7±1.7	2.5±2	-0.80 (-1.2 to -0.3)
- length of stay on general ward unit-days†	4.4±2.4	3.8±2.7	0.6 (-0.04 to 1.2)

¶ datas are presented as number (percentage) or mean±SD of patients

Odds ratios are presented for difference between rates and Mean difference are presented for others outcomes

*defining by non-invasive 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

‡ defining by FiO2 more than 21% rate (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 PICU stay

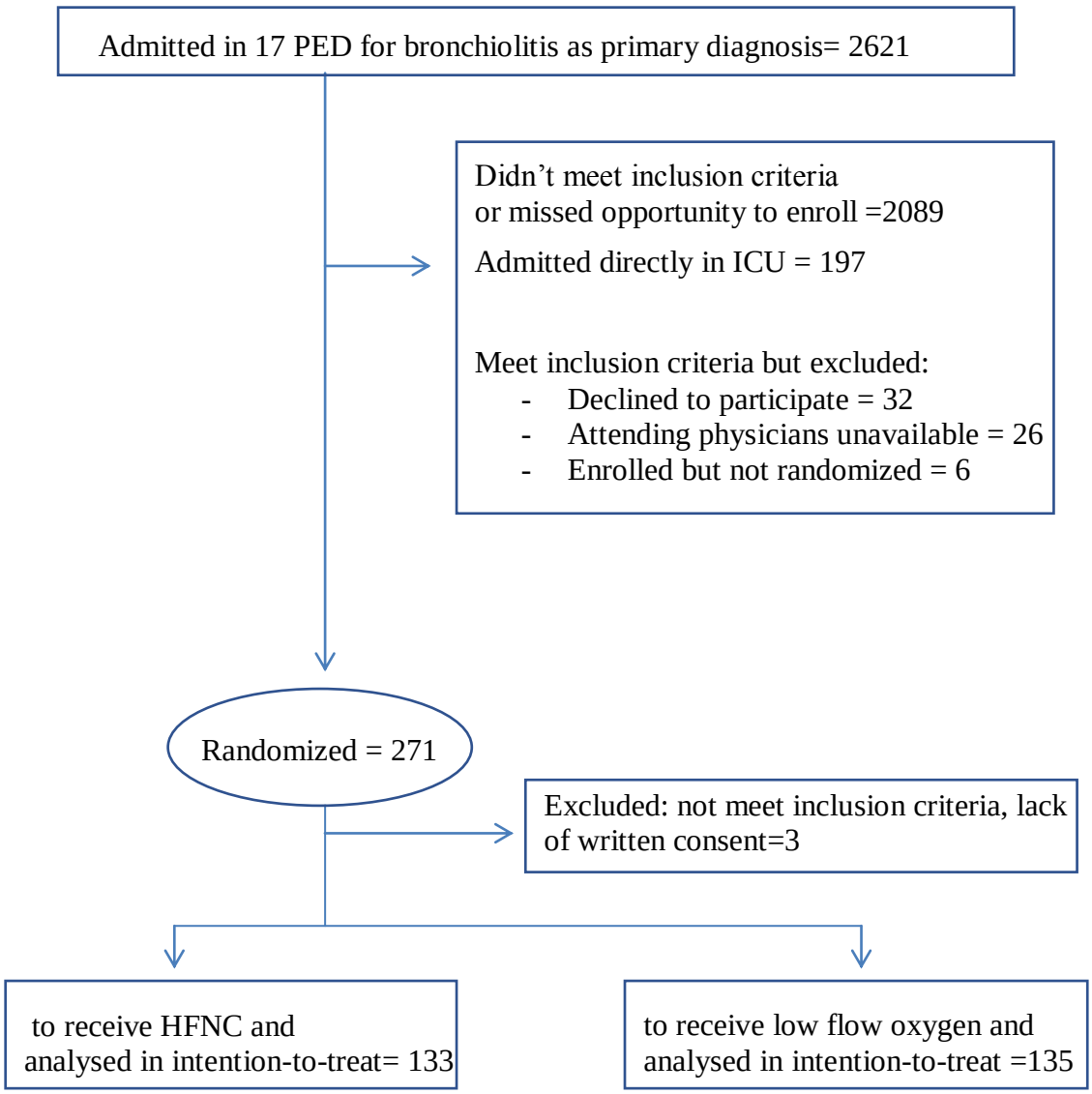
£ One patient in control group who failed and escalated on HFNC was kept on pediatric general ward

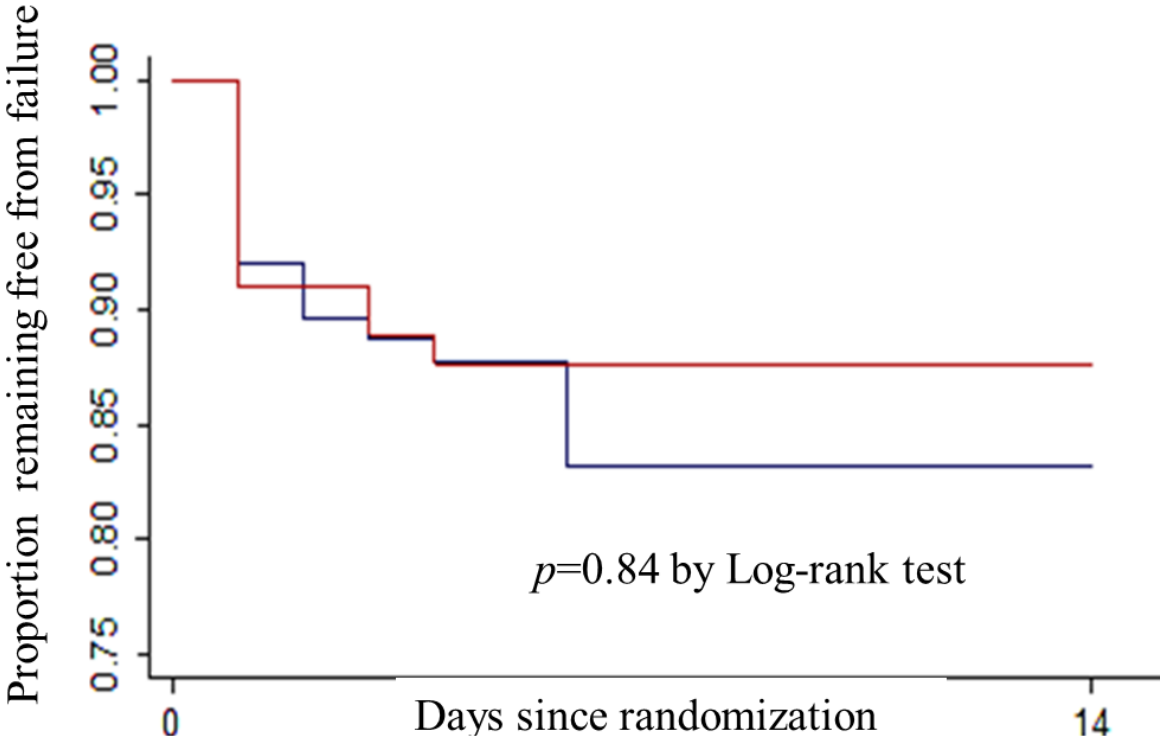
Table 3. Physiologic Variables and m-WCAS score at 1 Hour, and After 6 and 12-Hours after Randomization according to Group¶

Characteristics	HFNC group (N=133)	Control group (N=135)	Mean difference (95% CI)	P value
At H1				
RR- bpm	46±13	50±13	-4. (-7.5 to -0.9)	**0.01**
HR-bpm	151±18	151±16	0.3 (-3.9 to 4.6)	ns
SpO2-%	97±2	97±3	0.02 (-0.6 to 0.7)	ns
FiO2* or O2 flow rate†	25±5%	0.5±0.4 L/min		NA
delta m-WCA score	-0.098±0.22	-0.036±0.23	| -0.06 (-0.12 to -.004)	<**0.01**
Apnea events	1	1		ND
At H6				
RR-bpm	45±13	49±15	-3.6 (-7.2 to 0.004)	**0.05**
HR-bpm	152±17	151±18	1.2 (-3.1 to 5.6)	ns
SpO2-%	97±2	97±2	-0.04 (-0.6 to 0 .5)	ns
P(t)CO2, Mean (SD)-mmHg	44 ±7	48±10	-3.6 (-8.5 to 1.2)	ns
FiO2* or O2 flow rate†	26±6 %	0.5±0.3 L/min		NA
delta m-WCA score	-0.16±0.35	0.11±0.31	-0.05 (-0.1 to 0.03)	ns
Apnea events	0	0		ND
At H12				
RR-bpm	42±13	47±14	-4.8 (-8.3 to -1.2)	**0.01**
HR-bpm	146±18	145±18	1.5 (-3.1 to 6.1)	ns
SpO2-%	97±2	97±2	-0.3 (-0.9 to 0.2)	**ns**
FiO2* or O2 flow rate†	25±5%	0.5±0.4 L/min		NA
delta m-WCA score	-0.23±0.31	-0.15±0.38	-0.07 (-0.1 to 0.02)	ns

¶ datas are presented as number (percentage) or mean±SD of patients

* on HFNC group, †on control group, NA denote not applicable, ND denote not determined, m-WSCA score denote modified-Wood clinical asthma score.


Admitted in 17 PED for bronchiolitis as primary diagnosis= 2621
Didn't meet inclusion criteria
or missed opportunity to enroll =2089
Admitted directly in ICU = 197
Meet inclusion criteria but excluded:
- Declined to participate = 32
- Attending physicians unavailable = 26
- Enrolled but not randomized = 6
Randomized = 271
Excluded: not meet inclusion criteria, lack of written consent=3
to receive HFNC and
analysed in intention-to-treat= 133
to receive low flow oxygen and
analysed in intention-to-treat =135



Number at risk

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

Online-Only Supplements

eTable 1. Modified Wood clinical asthma score (mWCAS).

eTable 2. Severity at Failure and Reason for Failure according to Group.

eTable 1. Modified Wood clinical asthma score (m-WCAS).

	0	0,5	1	2
Cyanosis	SpO_2 >95% in room air	90%≤SpO_2<95% In room air	SpO_2>95% with FiO_2>21%	SpO_2< 95% with FiO_2>21%
Inspiratory breath	Normal	Slightly unequal	Unequal	Decreased or absent
Accessory muscles use	Absent	low	Moderate	Maximal
Expiratory wheezing	Absent	low	Moderate	Maximal
Cerebral function	Normal	Agited if disturbed	Depressed or agitated	Coma

The m-WCAS is a composite score assessing the severity of bronchiolitis through five components (cyanosis, inspiratory breath sounds, accessory muscles use, wheezing, and cerebral function). Each is rated from 0 to 2 for maximal value. A visual analog scale is used to standardize the scoring of accessory muscle use and wheezing.

eTable 2. Severity at Failure and Reason for Failure according to Group.

Characteristics	HFNC group (N=133)	Control group (N=135)	Mean difference (95% CI)	P value
Severity at failure				
no. (%)	19	27		
HR-bpm	160±18	159±18	0.8 (-10.3 to 12)	ns
RR-bpm	58±14	60±17	-1.5 (-11.1 to 8.05)	ns
SpO2-%	96±3	95±4	0.6 (-1.8 to 3.1)	ns
P(t)CO2, Mean (SD)-mmHg	53±10	66±9	-12.7 (-22.2 to -3.2)	**0.01**
FiO2* or O2 flow rate†	33±8%	1±0.7 L/min		NA
m-WCA score	5.5±1.2	4.7±0.8	0.7 (-0.005 to 1.4)	ns
Reason for failure‡				
Apnea episode (> 3/h)	0	1		ND
Increasing m-WCAS score (or > 6)	12	20		ns
Increasing P(t)CO2 (or > 70mmHg)	3	8		ns
FiO2 or O2 flow-rate exceeding 40% or 2L/min	9	8		NA
Apnea events	1	1		ND

* on HFNC group, †on control group, ‡ one or several, NA denote not applicable, ND not determined.

HFNC high-flow nasal cannula, m-WCAS modified Wood clinical asthma score