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Noninvasive Respiratory Support Weaning in Infants With Severe Bronchiolitis: High Flow Nasal Cannula May Reduce the Length of Stay

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ABSTRACT

Introduction: The aim is to describe weaning procedures, weaning failure rates, and predictors and consequences of weaning failure in infants admitted to pediatric intensive care units (PICUs) for severe bronchiolitis.

Methods: This is a multicenter prospective observational cohort study in five PICUs in French university hospitals. Consecutive infants aged 3 days to 6 months admitted between November 2020 and April 2022 with a clinical diagnosis of severe bronchiolitis requiring noninvasive ventilatory support by bilevel positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), or high-flow nasal cannula (HFNC).

Results: Demographic and clinical data were collected prospectively. Weaning strategies were classified as direct, HFNC for de-escalation, and gradual with decreasing support levels. Multivariate analysis was performed to identify independent predictors of weaning failure. Of the 135 included patients (median age 1 [1–2] months), 60 (44%), 49 (36%), and 26 (19%) were managed by HFNC-based, direct, and gradual weaning, respectively. Bronchiolitis severity was similar in the three groups. By multivariate analysis, predictors of weaning failure was gradual weaning (odds ratio, 10.56 [2.87–38.86], $p < 0.01$), while apnea at admission (0.26 [0.07–0.96], $p = 0.04$) and younger age (0.44 [0.23–0.84], $p = 0.02$) were protective factors. PICU length of stay was shorter with HFNC-based weaning (3.8 [1.9–5.4] days vs. 4.3 [3.0–6.9] and 5.1 [3.8–7.4] with direct and gradual weaning, respectively, $p = 0.02$).

Conclusions: Among patients with severe bronchiolitis, a weaning strategy using HFNC for de-escalation was associated with shorter PICU stays. Whether this method also decreases the risk of weaning failure deserves investigation.

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; PICU, pediatric intensive care unit.

1 | Introduction

Acute viral bronchiolitis is a major health issue in infants and young children throughout the world. Among hospitalized patients, 2%–6% develop acute respiratory failure requiring admission to the pediatric intensive care unit (PICU) [1–4]. The first-line treatment is then noninvasive ventilatory support using bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) [5]. High-flow nasal cannula (HFNC) therapy is often given in the more moderate forms, despite continuing uncertainty about optimal indications [5, 6].

Whereas the criteria for using noninvasive ventilatory support are relatively well agreed on, debate continues regarding the best criteria and strategy for weaning and their possible effects on outcomes [7]. Most published studies of these issues focused on weaning off HFNC in various conditions and used a single-center design [8–10]. The latest guidelines indicate a need for further research [11]. Using noninvasive ventilatory support longer than necessary may increase the risk of complications, PICU and hospital stay lengths, and healthcare costs. On the other hand, weaning too early may increase the risk of failure, morbidity rates, and the total duration of ventilation [12]. Determining the criteria for weaning initiation and identifying the best weaning strategy are, therefore, crucial. A 2023 clinical-practice consensus statement developed using the Delphi technique defined weaning and weaning failure and identified weaning-initiation criteria and weaning modalities in pediatric patients with acute disease [13].

The objectives of this multicenter prospective observational cohort study were to describe weaning procedures, weaning failure rates, and consequences of weaning failure and to identify predictors of weaning failure in neonates and infants admitted to PICUs for severe bronchiolitis.

2 | Methods

2.1 | Study Design

This multicenter prospective observational study was conducted from November 2020 to April 2022 in five PICUs in five French university-hospital centers. The procedures followed were in accordance with the ethical standards of French law on human experimentation and with the Helsinki Declaration of 1975.

The data were handled according to French MR-004 reference methodology and the study was registered with the French data protection authority (CNIL, #2205066v0 on August 18, 2018 for the study entitled "Sevrage de la ventilation non-invasive dans la bronchiolite aigue du nourrisson"). This methodology waived the need for written informed consent. This report complies with STROBE requirements (see Supporting Information Digital Content). The parents of each patient were informed of the study and asked whether they had any objections to the inclusion of their child.

2.2 | Study Population

Consecutive patients who were aged 3 days to 6 months and were admitted to one of the participating PICUs with a clinical diagnosis of bronchiolitis requiring noninvasive respiratory support (BiPAP, CPAP) within 24 h after PICU admission were included. Patients supported by HFNC were also included if they were finally switched to CPAP or BiPAP. Criteria for PICU admission and for initiating noninvasive ventilatory support were at the discretion of the attending physicians. In the French healthcare system, respiratory support can be initiated by transport teams and in some centers, in an emergency room.

Noninclusion criteria were long-term (i.e., home) BiPAP or CPAP support, underlying significant cardiac or neuromuscular disease, pneumothorax on the admission chest radiograph, gestational age of 36 weeks or less at birth, invasive mechanical ventilation before or after noninvasive ventilatory support, and unwillingness of the parents to have their child participate.

Patients were excluded from the analysis if there was significant missing data regarding the main outcome.

2.3 | Patient Management

2.3.1 | Noninvasive Ventilatory Support

BiPAP and CPAP were given using an ICU ventilator (Evita 2 or Evita XL, Dräger Medical, Lübeck, Germany or Servo-i or Servo-u, Maquet Critical Care AB, Solna, Sweden) with a facial or nasal interface. With BiPAP, pressure support ranged from +4 to +10 cmH_2O above positive expiratory airway pressure. CPAP was with a positive pressure of 7 cmH_2O. HFNC therapy was started at a flow rate of 2 L/kg/min with an ICU ventilator or a specific device (Airvo 2, Fisher and Paykel, Auckland, New Zealand). In none of the five participating hospitals was HFNC used in pediatric wards. Patient management was at the discretion of the clinical team.

2.4 | Weaning

Based on the recent clinical-practice consensus statement [13], we distinguished three weaning strategies (Figure 1): weaning,

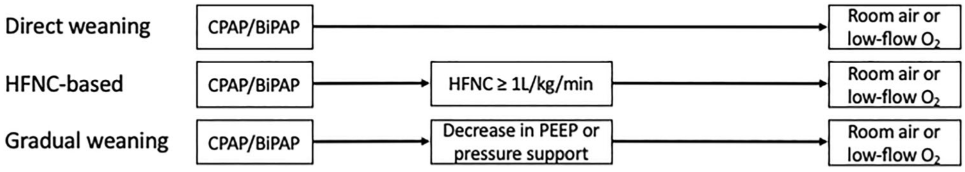

FIGURE 1 | Definitions of the three weaning strategies. BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; PEEP, positive end-expiratory pressure.

defined as switching from BiPAP or CPAP to room air or low-flow oxygen; HFNC-based weaning defined as using HFNC for de-escalation before switching to room air or low-flow oxygen; and gradual weaning, defined as gradually decreasing the level of support. In each patient, only the first weaning attempt was included in the analysis.

The main outcome was weaning failure defined as a need for (invasive or noninvasive) ventilatory support within 24 h after weaning [13]. None of the participating PICUs had weaning protocols but all had protocols to initiate ventilatory support. Both the time of weaning initiation and the weaning strategy were at the discretion of the attending intensivist.

2.5 | Data Collection

Standardized forms were used to collect age, sex, comorbidities, and clinical data during the PICU stay. Respiratory comorbidity was defined as any clinically significant neonatal lung disease. The Wang Bronchiolitis Severity Score (WBSS) [14] and modified Wood's Clinical Asthma Score (m-WCAS) [15] were recorded, as well as the hemodynamic and respiratory parameters, ventilatory mode and settings, medications, and laboratory data at PICU admission including venous pH and venous carbon dioxide ($PvCO_2$). We also collected the durations of ventilatory support and of weaning, whether weaning failed, and the PICU and hospital lengths of stay. Pneumothorax and interface-related skin lesions were recorded as complications of noninvasive ventilatory support.

2.6 | Statistical Analysis

Continuous variables were described as median [interquartile range] or mean ± SD depending on distribution and categorical variables as n (%). Analyses were performed on the population, separately in each of the three weaning-strategy groups (direct, HFNC-based, and gradual). The baseline characteristics and features at PICU admission were compared: for continuous variables, analysis of variance was performed if distribution was normal and the Kruskal–Wallis test otherwise, and for categorical variables, we used the chi-square test if applicable and Fisher's exact test otherwise.

Then, the proportions of patients with weaning failure and other short-term outcomes were compared across the three groups. To identify independent predictors of weaning failure, we performed a multivariate analysis using linear regression with backward stepwise elimination. For the model, we considered variables that were likely to influence the risk of weaning failure or were associated with the weaning strategy by univariate analysis (age, sex, apnea at PICU admission, FiO_2 at PICU admission, need for antibiotics, and FiO_2 and respiratory rate at weaning). Missing data were ignored.

All tests were two-sided and p values of less than 0.05 were considered significant. Statisticians at the Grenoble-Alpes University Hospital performed the statistical analyses using Stata version 18 (StataCorp, College Station, TX).

3 | Results

3.1 | Study Population

Of the 142 included patients, 7 were excluded due to insufficient data. No parent refused to allow their child to participate in the study. The analysis thus included 135 patients (72 girls), with a median age of 1 [1–2] month. Table 1 reports their main features. Severity of the respiratory illness as assessed based on the respiratory parameters and $PvCO_2$ values was similar in the three weaning-strategy groups.

3.2 | Weaning

The HFNC-based strategy was the most often used, with 60 (44.4%) patients, followed by direct weaning ($n = 49$, 36.3%), then by gradual weaning ($n = 26$, 19.3%). Importantly, disease severity was not significantly different across the three groups, except for pH (Table 1). Weaning failed in 25 (18.5%) of the 135 patients. Weaning failure was more common with gradual weaning (11/26, 42%) than with direct weaning (9/49, 18%) or HFNC-based weaning (5/60, 8%) ($p = 0.001$). We did not find any association between the risk of weaning failure and the maximum level of support required ($p = 0.71$).

Multivariate analysis identified one independent predictors of weaning failure, namely, gradual weaning (odds ratio [OR], 10.56; 95% confidence interval [95% CI], 2.87–38.86]; $p < 0.001$), and two protective factors, namely apnea at PICU admission (OR, 0.26; 95% CI, 0.07–0.96; $p = 0.04$), and younger age (OR, 0.44; 95% CI, 0.23–0.84; $p = 0.02$) (see Supporting Information Digital Content).

Median PICU length of stay was significantly shorter with HFNC-based weaning (3.8 [1.9–5.4] days) than with direct weaning (4.3 [3.0–6.9] days) or gradual weaning (5.1 [3.8–7.4] days) ($p = 0.02$) (Figure 2A). The noninvasive ventilatory support duration including (panel B) or excluding HFNC (panel C) did not differ according to the weaning strategy.

4 | Discussion

In a prospective 2-year cohort of 135 neonates and infants with severe bronchiolitis requiring PICU admission and noninvasive ventilatory support, an intermediate period on HFNC was the most common weaning strategy, followed by direct weaning, and then by gradual weaning. Weaning failure occurred in nearly a fifth of patients overall. Factor independently associated with weaning failure was gradual weaning, while apnea at PICU admission and younger age were protective factors. The median PICU length of stay was significantly shorter with HFNC-based weaning than with the other two strategies.

To our knowledge, few studies have focused on weaning off noninvasive ventilatory support in full-term neonates and infants. In a randomized trial, the duration of weaning off CPAP was not significantly shorter with de-escalation HFNC, but only patients born before 32 gestational weeks were included (17). A

TABLE 1 | Main features of the 135 study patients at admission.

		Data available[a]	Direct weaning $N = 49$	HFNC-based weaning $N = 60$	Gradual weaning $N = 26$	p value
Demographics	Female sex, n (%)		24 (49)	32 (53)	16 (62)	0.58
	Weight (kg), median [IQR]		4.1 [3.4–4.5]	4.0 [3.4–4.9]	3.9 [3.4–5.0]	0.49
	Age (months), median [IQR]		1 [0–2]	1 [1–2]	1 [1–2]	0.32
Comorbidities, n (%)	Respiratory		0	1 (2)	0	> 0.99
	Cardiac		0	1 (2)	0	> 0.99
	Neurologic		0	1 (2)	0	> 0.99
Virus, n (%)	RSV		35	49	19	0.18
	Other virus		8	10	3	
	None		6	1	4	
Clinical status at PICU admission	WBSS, mean ± SD	$N = 47$	7.7 ± 1.8	7.7 ± 1.5	8.5 ± 0.7	0.80
	m-WCAS, median [IQR]	$N = 118$	5 [3.5–6]	5 [4–6]	4 [3.5–5]	0.20
	Respiratory rate (/min), mean ± SD		54 ± 19.7	55 ± 14.2	56 ± 18.3	0.89
	Heart rate (/min), mean ± SD		162 ± 19.8	164 ± 20.8	165 ± 20.8	0.79
	Apnea, n (%) of patients		17 (35)	9 (15)	8 (31)	0.048
Ventilatory mode and settings at PICU admission	HFNC, n (%)		15 (31)	11 (18)	5 (19)	0.28
	CPAP, n (%)		25 (51)	34 (57)	16 (62)	0.67
	BiPAP, n (%)		9 (18)	15 (25)	5 (19)	0.67
	FiO_2 (%), median [IQR]		30 [25–40]	30 [28–40]	33 [25–40]	0.16
Laboratory data at PICU admission	Venous/capillary blood gas measurement, n (%)		32 (65)	47 (78)	16 (62)	0.18
	pH, mean ± SD		7.31 ± 0.07	7.36 ± 0.06	7.31 ± 0.05	< 0.001
	$PvCO_2$ (mmHg), mean ± SD		55.0 ± 10.7	51.3 ± 10.2	50.5 ± 13.3	0.26
Medical treatments at PICU admission, n (%)	Antibiotics		18 (37)	19 (32)	10 (39)	0.78
	Caffeine		6 (12)	3 (5)	2 (8)	0.39
	Inhaled bronchodilatators		2 (4)	2 (3)	0	0.83
	Sedatives		2 (4)	5 (8)	0	0.31

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, inspired fraction of oxygen; HFNC, high-flow nasal cannula; m-WCAS, modified Wood's clinical asthma score; $PvCO_2$, partial venous carbon dioxide pressure; RSV, respiratory syncitial virus; WBSS, Wang bronchiolitis severity score.
[a]When no number is given, the data were available for all 135 patients.

retrospective study included only patients on long-term non-invasive ventilatory support [16, 17]. This paucity of data is concerning, given that bronchiolitis is the leading cause of severe respiratory failure in infants in high-income countries [18]. In a single-center retrospective study of 95 infants, including 80 born at full term, the weaning failure rate was 12% [19]. Most patients were weaned using a step-down strategy, with switching from BiPAP to CPAP to HFNC. A survey done in three European countries, Canada, and Algeria found that de-escalation to CPAP was the most common strategy in patients on BiPAP, whereas direct weaning was used for slightly over half the patients on CPAP and all those on HFNC [20]. Of note, the latest clinical practice guidelines, published in 2023, make no mention of the weaning strategy [11].

Ventilatory support practices for infants with bronchiolitis vary widely [21]. Our study demonstrates that weaning practices are also heterogeneous. We defined three weaning strategies based on a 2021 survey of French PICU physicians [20] and an observational study [19]. Interestingly, HFNC for de-escalation

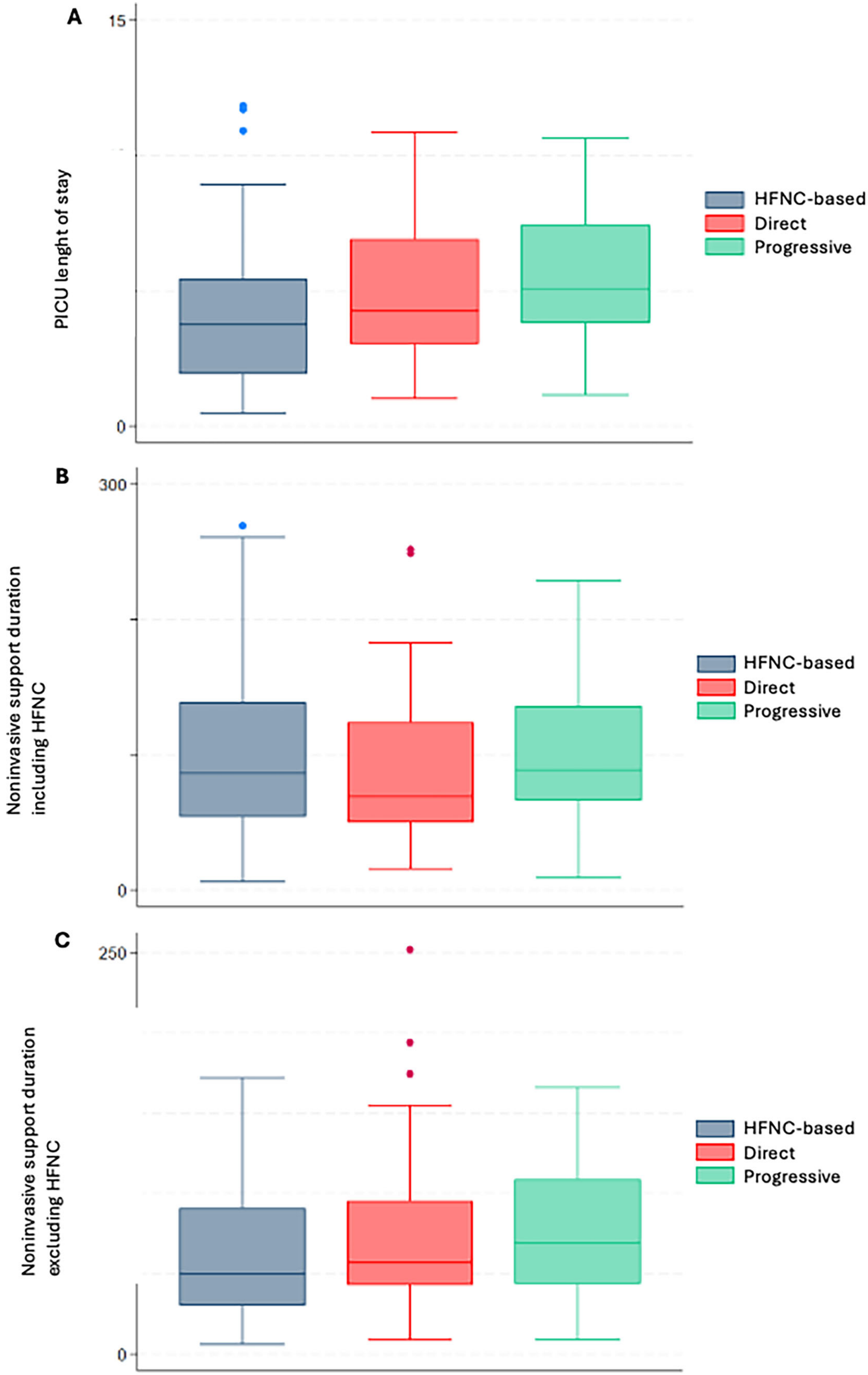

FIGURE 2 | Outcomes according to the type of weaning strategy. (A) PICU lenght of stay, (B) Noninvasive support duration including HFNC, and (C) Noninvasive support duration excluding HFNC. [Color figure can be viewed at wileyonlinelibrary.com]

was the most common weaning strategy, despite continuing uncertainty about the role for HFNC in managing infants with bronchiolitis [22]. HFNC de-escalation may improve patient comfort and may also decrease the PICU stay length in centers where HFNC is used on wards. Although this was not the case in any of our five study centers, and despite the similar illness severity and duration of noninvasive ventilatory support across the three groups, HFNC-based weaning was associated with a significantly shorter PICU stay length. Moreover, the smaller proportion of patients with weaning failure in the HFNC-based group was not statistically significant, which may be due to the small sample size. HFNC de-escalation would therefore seem to deserve further evaluation, notably to determine the optimal criteria for switching from BiPAP or CPAP to HFNC and to assess potential effects on failure rates and PICU stay length. Of note, hospital stay length did not differ across weaning strategies, perhaps due to persistent dependency on enteral feeding after PICU discharge. However, we acknowledge that the PICU length of stay may be influenced by several other factors, including the perceived clinical status of the patient at the time of starting weaning, the mode and settings of ventilatory support, and the patient factors.

The weaning failure rate was 18.5% in our cohort, in keeping with findings from a cross-sectional study in children younger than 2 years [23]. A study in the same age group as ours (younger than 6 months) had a lower failure rate of 11.6% [19]. In contrast to endotracheal mechanical ventilation, noninvasive ventilatory support can easily be restarted should weaning failure occur. Thus, intensivists may decide to attempt weaning at an earlier stage of the respiratory function improvement. Nonetheless, we previously reported that failure of weaning off noninvasive ventilatory support was associated with longer PICU and hospital stays [19].

Interestingly, apnea at PICU admission and younger age independently predicted weaning success. These two features are part of a specific clinical bronchiolitis phenotype [24]. Whether the weaning strategy should be tailored to the clinical bronchiolitis phenotype deserves investigation.

One limitation of this study is the observational design. The participating PICUs had no protocol for choosing the weaning strategy or determining when to initiate weaning. Some data may suggest a difference in terms of admission criteria between centers but overall, patient characteristics do not seem to differ between participating centers. Since members from those six centers were involved in the recent French recommendations for severe bronchiolitis management, we may hope that clinical practices should not differ significantly between those centers. Nonetheless, this design reflects the current dearth of data on which to base these choices. Moreover, illness severity was not significantly different across the three groups, except for pH, which we considered as non-clinically significant. Second, despite the prospective data collection, data for some variables were missing for a substantial number of patients. Third, we categorized the weaning strategies based on a single survey. Again, this reflects the paucity of published data. For the gradual-weaning category, we did not collect the changes in support level. Another limitation is the fact that the sample size was initially calculated based on two weaning strategies, while we considered three strategies in the analysis. Overall, the sample size was relatively small. Finally, we acknowledge that the choice of weaning strategy depends on the ventilatory mode and settings at the point of starting weaning. A strength of our study is the recruitment at five PICUs, over two consecutive bronchiolitis seasons, which supports the general applicability of our findings. Despite the limited sample size, our multivariate analysis identified one independent predictor of weaning failure and two protective factors. This constitutes a pilot study before building a randomized controlled study to identify which weaning strategy should be performed.

5 | Conclusion

This multicenter prospective study evidenced considerable variability in weaning strategies. Younger age and apneas at PICU admission seemed to be protective factors of weaning failure. HFNC for de-escalation was significantly associated with a shorter PICU stay. A future randomized trials is warranted to definitively determine which weaning strategy provides the best outcomes.

Author Contributions

G.M., C.M., J.C., and F.B. wrote the manuscript. C.M., J.G., J.E.P., and F.B. collected the data. A.E. and D.S. performed the analysis. The manuscript was reviewed by all the authors.

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Ethics Statement

The study was approved according to the reference methodology MR-003, which waived the need for written informed consent, in compliance with French law. The parents of each patient were informed of the study and asked whether they objected to participation of their child.

Consent

The authors have nothing to report.

Conflicts of Interest

F.B. has received nonfinancial support from Fisher & Paykel, Dräger, and Sedana Medical. The other authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.